Effectiveness of Syringe Services Programs

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PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to conduct timely, rigorous, and independent systematic reviews to support VA clinicians, program leadership, and policymakers improve the health of Veterans. ESP reviews have been used to develop evidence-informed clinical policies, practice guidelines, and performance measures; to guide implementation of programs and services that improve Veterans' health and wellbeing; and to set the direction of research to close important evidence gaps. Four ESP Centers are located across the US. Centers are led by recognized experts in evidence synthesis, often with roles as practicing VA clinicians. The Coordinating Center, located in Portland, Oregon, manages program operations, ensures methodological consistency and quality of products, engages with stakeholders, and addresses urgent evidence synthesis needs.

Nominations of review topics are solicited several times each year and submitted via the ESP website. Topics are selected based on the availability of relevant evidence and the likelihood that a review on the topic would be feasible and have broad utility across the VA system. If selected, topics are refined with input from Operational Partners (below), ESP staff, and additional subject matter experts. Draft ESP reviews undergo external peer review to ensure they are methodologically sound, unbiased, and include all important evidence on the topic. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. In seeking broad expertise and perspectives during review development, conflicting viewpoints are common and often result in productive scientific discourse that improves the relevance and rigor of the review. The ESP works to balance divergent views and to manage or mitigate potential conflicts of interest.

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Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

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Disclosures

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The findings and conclusions in this document are those of the author(s) who are responsible for its contents and do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. The final research questions, methodology, and/or conclusions may not necessarily represent the views of contributing operational and content experts. No investigators have affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

Executive Summary

KEY FINDINGS

- Despite some gaps, the evidence demonstrating the potential benefits of SSPs and relative lack of harms is sufficient to support SSP implementation when possible.
- SSP utilization likely lowers HIV transmission and reduces injection risk behaviors, and may lower HCV transmission, promote carrying naloxone, increase exposure to overdose education, and facilitate referral to and enrollment in treatment services. SSP use and presence in communities does not appear to increase injection frequency, unsafe syringe disposal practices, or neighborhood crime rates.
- Preliminary evidence suggests that combined SSP and OUD treatment programs may improve some outcomes more than either intervention alone. Coordinated or co-located SSP and OUD treatment interventions represent a promising area for future research.

Substance use-related harms including drug overdose deaths and new cases of human immunodeficiency virus (HIV) and hepatitis C (HCV) are increasing in the US. Syringe services programs (SSPs) started in the 1980s as community-based efforts to distribute sterile syringes and provide safe injection information to people who inject drugs (PWID) in response to rising HIV infection rates. SSPs are guided by harm reduction principles, which aim to mitigate the negative consequences of drug use. The term *SSP* broadly refers to the provision of sterile syringes and other supplies and is inclusive of any setting that provides these supplies for the intended injection of drugs. The present report is an attempt to provide an overall picture of what is known about the benefits and potential harms of SSPs, which has been an active area of research for the past 4 decades. This report was requested by the VA Offices of Mental Health and Suicide Prevention, Research and Development, and Specialty Care Services to inform VA efforts to meet the goals of the Office of National Drug Control Policy and to implement best practices for harm reduction in VHA settings.

Our search identified 399 potentially relevant articles after deduplication and title and abstract screening. We relied on results of a 2022 review of reviews to describe the effectiveness of SSPs on HIV and HCV transmission, as well as injection risk behaviors. We prioritized synthesis of 48 primary studies to evaluate the potential benefits and harms of SSPs related to injection frequency, naloxone distribution and overdose education, linkage to substance use treatment and utilization of treatment services, syringe disposal practices, and neighborhood crime rates. We also synthesized available evidence on whether outcomes vary by syringe exchange model (needs-based versus 1-for-1) or presence/absence of program components.

The 2022 review of reviews found sufficient evidence that SSPs prevent HIV transmission among PWID and tentative evidence that SSPs prevent HCV transmission. Studies of HCV prevention had less consistent results compared to studies of HIV prevention, but it is unknown whether the weaker benefit in terms of HCV prevention is primarily due to study factors (such as the ways SSP use was defined and measured in studies evaluating HCV transmission) or differences in HIV and HCV transmissibility. Additionally, the relatively recent availability of curative therapy options for HCV is likely altering the epidemiology of HCV in ways that have not yet been reflected in available evidence. The same 2022 review of reviews found sufficient evidence that SSP use reduced injection risk behaviors, an important intermediate outcome when considering that a primary aim of SSPs is to prevent infectious disease transmission.

Importantly, SSP use does not appear to increase injection frequency, unsafe disposal of syringes, or neighborhood crime rates. SSP use may be associated with increased treatment linkage and/or use of treatment services among PWID compared to no SSP use (or less use). Preliminary evidence suggests that coordinated or co-located SSPs and programs offering OUD treatment may have improved outcomes relative to either program alone, which represents a promising area for future research.

Studies of public health interventions in real-world settings often must rely on observational research methods that are intrinsically less rigorous than study designs available in clinical contexts. These methodological limitations lower the strength of available evidence for individual SSP outcomes (listed below). However, when looking across outcomes, the preponderance of evidence demonstrating the potential benefits of SSPs and relative lack of harms is more than sufficient to support SSP implementation when possible.

ES Table. Summary of Evidence

Outcome	Evidence	Findings
HIV transmission	1 RoR[1]	SSPs likely prevent HIV transmission.
HCV transmission	1 RoR[1]	SSPs may prevent HCV transmission. Coordinated or co-located SSPs and programs offering OUD treatment may have improved outcomes relative to either program alone.
Injection risk behaviors	1 RoR[1] 1 SR[2]	SSPs likely reduce injection risk behaviors. Use of SSPs offering needs-based or greater than 1-for-1 syringe exchange may be associated with a reduction in syringe re-use compared to use of SSPs with 1-for-1 syringe exchange polices or caps on the number of syringes dispensed.
Injection frequency	1 RCT,[3] 6 cohort,[4–9] and 9 pre-post[10–18] studies	SSP use does not appear to be associated with an increase in injection frequency.
Naloxone distribution	1 serial cross-sectional[19] and 4 cross-sectional[20–23] studies	SSP use may be associated with higher rates of carrying naloxone.
Overdose education	2 cross-sectional studies[21,24]	SSP use may be associated with receipt of overdose education.
Linkage to SUD treatment and utilization of treatment services	6 cohort[4,5,25–28] and 3 pre-post[11,16,17] studies	SSP use may be associated with increased treatment linkage and/or use of treatment services compared to no SSP use (or less use).
Syringe disposal	1 RCT,[29] 2 pre-post,[16,17] 11 cross-sectional,[30–40] and 7 ecological[41–47] studies	SSP use and/or presence of an SSP does not appear to be associated with an increase in unsafe syringe disposal practices.
Neighborhood crime rates	2 ecological studies[48,49]	Presence of an SSP does not appear to be associated with an increase in neighborhood crime rates.

Abbreviations. OUD=opioid use disorder; PWID=people who inject drugs; RCT=randomized controlled trial; RoR= review of reviews; SSP=syringe services program.

Main Report

Evidence Synthesis Program

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ABBREVIATIONS TABLE

AHRQ	Agency for Healthcare Research and Quality
AIDS	Acquired immunodeficiency syndrome
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IDU	Injection drug use
IRB	Injection risk behavior
KQ	Key question
OAT	Opioid agonist therapy
OR	Odds ratio
OUD	Opioid use disorder
PWID	People who inject drugs
RCT	Randomized controlled trial
RoR	Review of reviews
RR	Risk ratio
SSP	Syringe services program
SR	Systematic review
SUD	Substance use disorder
US	United States
VA	Department of Veterans Affairs
VHA	Veterans Health Administration
WHO	World Health Organization

BACKGROUND

The US Centers for Disease Control and Prevention (CDC) predicts that the total number of drug overdose deaths in the 12-month period that ended in February 2023 will be nearly 110,000.[50,51] While the increase in drug-related overdose deaths in the early 2000s was first attributed to prescription opioids and later to heroin use, the current trend of drug-related deaths is attributed to use of illicit synthetic opioids (*eg*, fentanyl and fentanyl analogs) as well as stimulants (*eg*, methamphetamine and cocaine) and exposure to these drugs in combination.[52] From 2013 to 2019, the synthetic opioid-involved death rate increased by 1,040% and the stimulant-involved death rate increased by 317%.[53]

The extent to which US Veterans use substances with high risk of overdose has not been well studied,[54] but deaths related to opioids have mirrored the rise seen in the general population.[55] Other substance use-related harms, such as the transmission of bloodborne pathogens via nonsterile syringes or other drug injection supplies, have also been increasing alongside drug overdose deaths. In 2014, rates of HIV infection in the US began to increase among persons who inject drugs for the first time in 2 decades.[56] Between 2013 and 2020, the incidence of acute hepatitis C (HCV) infection doubled.[57] In response to these trends, VHA has implemented several initiatives to reduce substance use-related harms, including expanding access to medications to treat opioid use disorder (OUD), providing naloxone rescue kits to Veterans at risk of overdose, and developing guidance for VHA health care facilities to develop syringe services programs (SSPs) to provide sterile syringes and other supplies.[58,59]

SSPs, which have also been referred to as needle exchanges, were first implemented in European countries and Australia in the 1980s as community-based efforts to distribute sterile syringes and provide safe injection information to people who inject drugs (PWID) in response to rising HIV infection rates.[60] These programs are guided by the principles of *harm reduction*, which has been defined as "a set of practical strategies and ideas aimed at reducing negative consequences associated with drug use."[61,62] The term *SSP* broadly refers to the provision of sterile syringes and other supplies and is inclusive of any setting that provides these supplies for the intended injection of drugs (including fixed locations, mobile units, and pharmacies).[62]

SSPs can vary widely in terms of their delivery models as well as the types and extent of additional health care services they provide.[63] SSPs with comprehensive services may offer naloxone and overdose education, fentanyl test strips, testing for infectious disease, vaccinations, linkages to addiction treatment, and (less commonly) medications for OUD.[63,64] These services are sometimes referred to collectively as *wraparound services* to emphasize that they are in addition to the core service of providing sterile syringes and supplies. In some cases, SSPs exclusively offering injection supplies may distribute these supplies by mail-order or through pharmacies.

In the US, public support for SSPs has varied regionally and over time. A variety of concerns about SSPs have emerged over the past several decades, including that SSPs promote or facilitate drug use, increase the frequency of injection drug use, attract PWID to communities where SSPs are located, risk public health due to unsafe syringe disposal, increase neighborhood crime, and divert funding away from addiction treatment.[62,65] Starting in the 1980s, many states prohibited SSPs or passed laws criminalizing the possession and distribution of syringes for purposes of illicit drug use, and the federal government previously implemented a near-total ban on the use of federal funds to support SSPs.[65] Whether SSPs are allowed to provide PWID with syringes based on need, rather than via 1-for-1 exchange, has also been a source of controversy with rules varying by state.[66]

While many restrictions were gradually rescinded starting in 2015 in response to increasing HIV and HCV infections in rural areas, an inconsistent legal framework and relative lack of public funding has limited the spread of SSPs in the US.[67,68] According to the North American Syringe Exchange Network (NASEN) directory of SSPs[69] (which relies on voluntary information sharing and is not a comprehensive list), the US currently has approximately 500 SSPs unevenly distributed across the country. For example, California has 58 SSPs and Kentucky has 45 listed on the NASEN website, while Kansas, Mississippi, Nebraska, South Dakota, and Wyoming have none.

VA currently offers SSPs in several locations including Danville, IL, Orlando, FL, and San Francisco, CA.[70] The number of programs is expected to increase in response to recommendations from VHA leadership that medical centers develop SSPs or otherwise ensure Veterans enrolled in VHA care have access to SSPs where not prohibited by state, county, or local law. Through VHA initiatives including the Pain Management, Opioid Safety and Prescription Drug Monitoring Program (PMOP),[58] VA facilitates have received funding and other supports to develop local SSPs.

Important changes in substance use trends, approaches to substance use prevention and treatment, public awareness of substance use harms, and legal and regulatory environments have occurred over the past 4 decades. Moreover, epidemiological features of HIV and HCV infection, approaches to prevention, and options for treatment of these diseases have evolved over time. A result of these changes and developments is a large and complex evidence base on SSPs. The present report is an attempt to provide an overall picture of what is known about the benefits and potential harms of SSPs. This report was requested by the VA Offices of Mental Health and Suicide Prevention, Research and Development, and Specialty Care Services to inform VA efforts to meet the goals of the Office of National Drug Control Policy[71] and to implement best practices for harm reduction in VHA settings.

METHODS

REGISTRATION AND REVIEW

A preregistered protocol for this review can be found on the PROSPERO international prospective register of systematic reviews (CRD42023438525).

KEY QUESTIONS AND ELIGIBILITY CRITERIA

The following key questions were the focus of this review:

Key Question 1	What are the benefits and harms of syringe services programs?
Key Question 1a	Do benefits and harms of syringe services programs vary by exchange model (needs-based vs 1-for-1) or presence/absence of program components?

Study eligibility criteria are shown in the table below. Systematic reviews were required to meet predefined methodological criteria established by the AHRQ Evidence-based Practice Program[72] to merit inclusion: 1) have an explicit and adequate search, 2) apply predefined eligibility criteria to select studies, 3) conduct risk of bias assessment for included studies, and 4) present a synthesis of results.

Population	Adults at risk for substance use-related harms.
Intervention	Syringe services programs. The primary intervention should be dispensing of sterile syringes, but programs may also include other components such as naloxone distribution, infectious disease testing, education on overdose prevention, safer injection practices, and/or infectious disease prevention, and/or referral to treatment and/or prevention services. The efficacy of these components as standalone interventions will not be evaluated.
Comparator	Any comparator or no comparator (*ie*, pre-post studies).
Outcomes	HIV/HCV prevalence or incidence, injection risk behaviors (sharing, borrowing, lending, reuse, or unsafe disposal of syringes); amount, speed, or frequency of injection drug use; naloxone distribution/use, knowledge of overdose risk; linkage to treatment for substance use disorder(s), HIV/HCV, HIV pre-exposure prophylaxis, or other medical needs; utilization of referred services; neighborhood crime rates or property values.
Study Design	Any, but we may prioritize studies using a best-evidence approach. Existing systematic reviews may be included to address some outcomes.

We did not examine primary studies for a given outcome when we identified a recent, rigorously conducted systematic review that included that outcome. This was the case for the outcomes of HIV/HCV prevalence and incidence and injection risk behaviors, which were covered in a recent review of reviews.[1] Similarly, we identified a 2010 systematic review[2] comparing SSP models and therefore restricted inclusion of primary studies relevant to Key Question 1a to more recent studies not included in that review.

SEARCHING AND SCREENING

To identify articles relevant to the key questions, a research librarian searched Ovid MEDLINE, CINAHL, PsycINFO, and the Cochrane Database of Systematic Reviews through March 2023 using terms for *syringe services programs* (see Appendix for complete search strategies). Additional

citations were identified from grey literature searches and hand-searching reference lists of included studies. The Cochrane Central Register of Controlled Trials was searched for underway studies. English-language titles, abstracts, and full-text articles were independently reviewed by 2 investigators, and disagreements were resolved by consensus.

DATA ABSTRACTION AND RISK OF BIAS ASSESSMENT

Effect information and population, intervention, and comparator characteristics were abstracted from all included studies. The internal validity (risk of bias) of each study was rated using the Cochrane risk of bias tools for systematic reviews,[73] randomized controlled trials,[74] and nonrandomized comparison studies.[75] We did not assess risk of bias of cross-sectional studies individually. All data abstraction and internal validity ratings were first completed by 1 investigator and then checked by another; disagreements were resolved by consensus or discussion with a third investigator (see Appendix for risk of bias ratings).

SYNTHESIS

We synthesized studies narratively using a "best evidence" approach, meaning that we focused on the studies most germane to our Key Questions and of the highest methodological quality.[76] We organized findings by outcome. Because we identified a recent, rigorously conducted review of reviews[1] on HIV/HCV prevalence and incidence and injection risk behaviors, we relied on syntheses from this review for these outcomes. For included primary studies, we prioritized evidence from longitudinal studies when available.

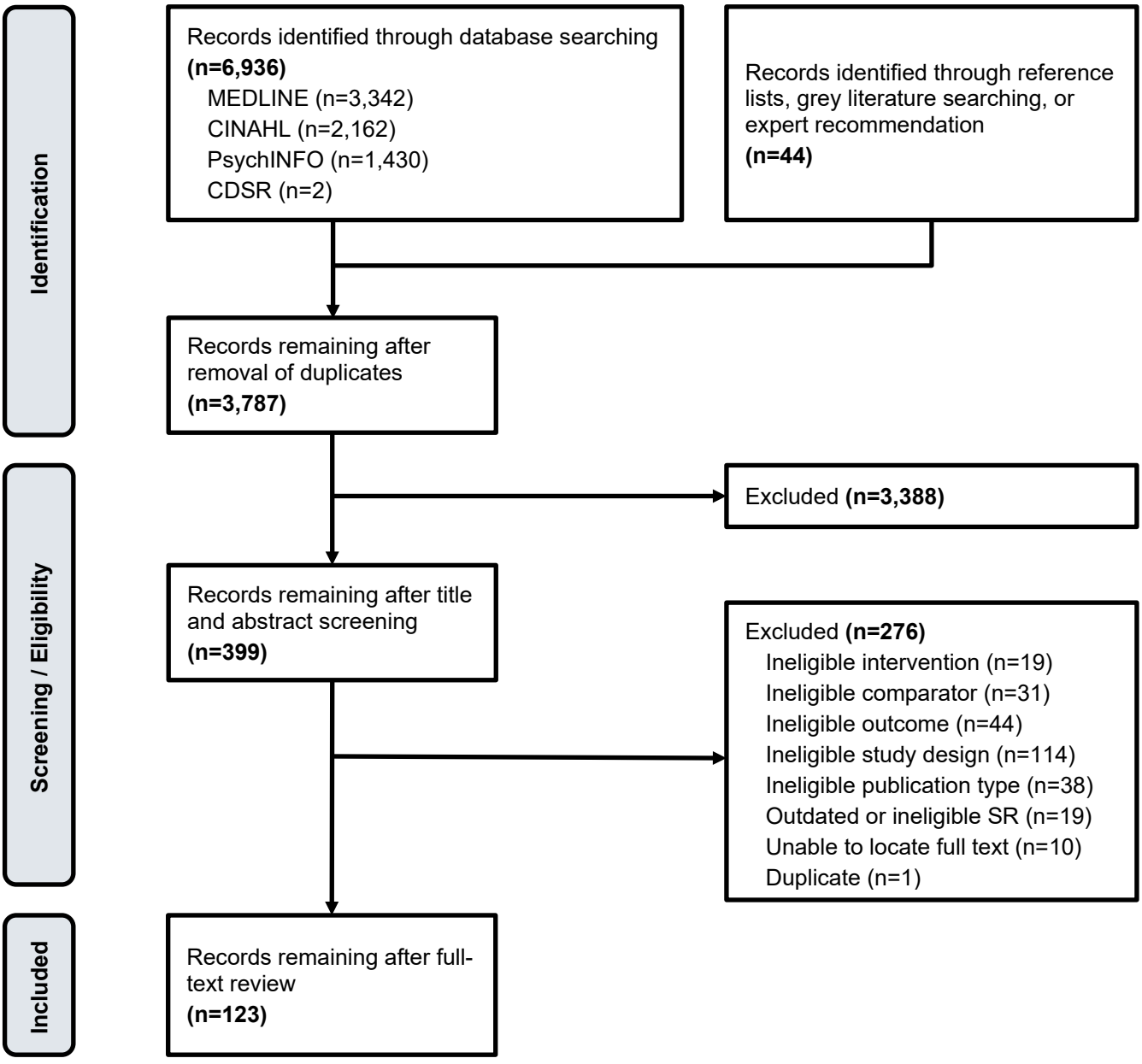
Strength of Evidence

After synthesizing available evidence, we rated the strength of evidence for each Key Question 1 outcome based on the methodology and risks of bias of available studies, the consistency and certainty of findings, and the directness of outcomes (whether reported outcomes are relevant to patients and providers).[77] For the outcomes of HIV/HCV prevalence and incidence and injection risk behaviors, we report the strength of evidence conclusions from the review of reviews described above.[1] For other outcomes, we applied the following general algorithm: *high strength* evidence consisted of multiple, large studies with low risk of bias, consistent and precise findings, and clinically relevant outcomes; *moderate strength* evidence consisted of multiple studies with low to unclear risk of bias, consistent and precise findings, and clinically relevant outcomes; *low strength* evidence consisted of multiple small or moderate-size studies, with unclear to high risk of bias, and inconsistent or imprecise findings; and *insufficient* evidence consisted of a single study or several small studies with an unclear or high risk of bias or no available studies.

RESULTS

LITERATURE FLOW DIAGRAM

The literature flow diagram summarizes the results of the study selection process. A full list of excluded studies is provided in the Appendix.



Notes. 17 SRs in 18 records; 100 primary studies in 105 records.

Abbreviations. CDSR=Cochrane Database of Systematic Reviews; CINAHL=Cumulative Index of Nursing and Allied Health.

Our search identified 399 potentially relevant articles after deduplication and title and abstract screening. Of these, 100 primary studies (in 105 publications) met eligibility criteria. We included 17 relevant SRs (in 18 publications; see Appendix for full list) and prioritized 2 that we determined were the most recent and comprehensive, a review of reviews[1] of HIV/HCV transmission and injection risk behaviors and a systematic review[2] comparing different approaches to the organization and delivery of SSPs. Both reviews were assessed as low risk of bias overall. The primary methodological limitation of the review of reviews[1] of HIV/HCV transmission and injection risk behaviors was that risk of bias of included primary studies was not assessed using an established assessment tool. Instead, the authors relied on study design as a proxy for risk of bias. However, risk of bias of included systematic reviews was assessed using a formal assessment tool. The primary methodological limitation of the review of SSP approaches[2] was that methodological quality was not addressed within the narrative synthesis. However, assessment of study quality was conducted and addressed in the discussion.

Review of Reviews on HIV/HCV Transmission and Injection Risk Behaviors

A 2022 review of reviews[1] on HIV/HCV transmission and injection risk behaviors was an update of a 2010 review of reviews[78] on the same topic. These reviews were broad in scope and included several other harm reduction interventions in addition to SSPs (*eg*, opioid agonist therapy). For the 2022 update, the authors used a stepwise approach to search the literature for new evidence. Specifically, they conducted an initial search for systematic reviews on a given intervention and outcome before proceeding to searches of the primary literature, and only searched the primary literature when evidence identified in systematic reviews was considered insufficient. The authors evaluated the quality of systematic reviews using the AMSTAR-2[79] tool and used a pragmatic approach to critical appraisal of primary studies by using study design as a surrogate for quality. Statements regarding the effectiveness of SSPs on preventing HIV/HCV transmission and mitigating injection risk behaviors were categorized as "sufficient," "tentative," or "insufficient" based on the available evidence.

HIV AND HCV TRANSMISSION

The 2022 review of reviews[1] described above found sufficient evidence that SSPs prevent HIV transmission among PWID (Table 1). This conclusion was based on findings from a 2014 systematic review and meta-analysis[80] of 12 primary studies (10 cohorts, 1 case-control, 1 cross-sectional). A meta-analysis of the 6 higher-quality studies indicated that SSPs are associated with significantly lower risk of HIV transmission (pooled risk ratio [RR] = 0.42, 95% CI [0.22, 0.81]). When the 6 low-quality studies were included, the risk reduction was somewhat smaller and bordered on significance (pooled RR = 0.66, 95% CI [0.43, 1.01]).

The same 2022 review of reviews[1] found tentative evidence that SSPs prevent HCV transmission among PWID. This conclusion was primarily informed by a Cochrane systematic review and meta-analysis[81] of primary studies comparing HCV transmission among individuals with high SSP coverage, defined as regular SSP attendance or at least 100% syringe coverage (having at least the supply needed to use a new needle and syringe for every injection), and those with low or no SSP coverage. Pooling adjusted estimates from 5 studies indicated a small and nonsignificant impact of SSP coverage on HCV transmission risk (pooled RR = 0.79, 95% CI [0.39, 1.61]). In contrast, when the analysis was limited to 2 studies that used syringe coverage as the measure of sterile syringe use (rather than SSP attendance), high SSP coverage was associated with a 76% reduction in HCV transmission risk (pooled RR = 0.24, 95% CI [0.09, 0.62]). Findings from additional primary studies were mixed and did not inform the authors' overall evidence statement.

INJECTION RISK BEHAVIORS

The same 2022 review of reviews[1] found sufficient evidence that SSPs reduce injection risk behaviors. This conclusion was informed by the authors' earlier 2010 review of reviews[78] in which evidence from 3 reviews[82–84] of 43 primary studies supported the effectiveness of SSPs in reducing injection risk behaviors. No further literature searching was conducted in 2022 given the already-sufficient level of evidence.

Table 1. Evidence Statements from 2022 Review of Reviews[1] on the Effect of SSP Utilization[a] on HIV/HCV Transmission and Injection Risk Behaviors

Outcome	Evidence[b]	Synthesis	Evidence Statement
HIV transmission	1 review[80] with a meta-analysis of 12 studies	Pooled effect size was equivocal when all studies were included; meta-analysis only including 6 higher quality studies found a 58% reduction in risk of HIV associated with use of SSP (RR = 0.42, 95% CI [0.22, 0.81]).	There is **sufficient** evidence that SSP use is effective in the prevention of HIV transmission among PWID.
HCV transmission	1 review[81] of 15 studies; 5 primary studies	A meta-analysis of 5 studies found an equivocal pooled effect (RR = 0.79, 95% CI [0.39, 1.61]); when meta-analysis was limited to 2 studies that used syringe coverage as the measure of sterile syringe use (rather than SSP attendance), the effect size was consistent with a 76% reduction in HCV incidence (RR = 0.24, 95% CI [0.09, 0.62]). Findings from additional primary studies were mixed.	There is **tentative** evidence to support the effectiveness of SSPs in the prevention of HCV transmission among PWID.
Injection risk behaviors[c]	3 reviews[82–84] of 43 primary studies (21 cohort studies, 21 cross-sectional studies, 1 ecological study)	Clear statement of evidence in support of SSPs from 2 SRs and consistent evidence from primary studies (39 positive studies, 1 negative, 1 no association).	There is **sufficient** review-level evidence to support the effectiveness of SSPs in reducing self-reported injection risk behaviors among PWID.

Notes. [a] SSP utilization compared with non-attendance or low SSP utilization; [b] Evidence from 2022 review of reviews update covering 2011-2020; [c] Level of evidence was sufficient in 2010 review of reviews and no update was undertaken.

Abbreviations. CI=confidence interval; HIV=human immunodeficiency virus; OR=odds ratio; PWID=people who inject drugs; SSP=syringe services program; RR=risk ratio.

Overview of Included Primary Studies

We identified 100 primary studies addressing the remaining outcomes of interest. While 69 studies evaluated injection frequency, we prioritized 16 studies with longitudinal data. Similarly, we identified 16 studies evaluating linkages to treatment and utilization of referred treatment services but prioritized synthesis of 9 studies with longitudinal data. All of these studies evaluated linkage to drug treatment or drug detoxification. We did not identify any studies evaluating whether SSP use is associated with referral to other forms of treatment, such as treatment for HIV or HCV. Of the remaining outcomes, 21 studies (1 RCT, 2 pre-post, 11 cross-sectional, and 7 ecological studies with outcomes that were assessed at a population level) reported on unsafe disposal of syringes, 5 cross-sectional studies reported on naloxone distribution or use, 2 cross-sectional studies reported on knowledge of overdose risk, 2 ecological studies reported on neighborhood crime rates, and 2 RCTs compared SSPs with different exchange models or program components. Exposures and outcomes were defined differently across studies. Most studies relied on participant self-report of SSP use or attendance, injection risk behaviors, and injection frequency. In total, we prioritized synthesis of 48 primary studies (see Appendix). We identified 2 underway studies (see Appendix).

Most studies were conducted in large US cities, and more studies were conducted in Baltimore, MD than in any other city. Eight were conducted outside the US (2 in Canada,[15,39] 3 in the UK,[11,12,23] 1 in Australia,[13] 1 in the Netherlands,[5] and 1 in Sweden[85]). Four studies[14,19,20,34] were conducted within a rural setting (West Virginia, Indiana, or Ohio), and 5 studies[12,13,18,23,31] were conducted within both urban and rural settings. The median sample size across studies was 431 (range: 54 – 6,321). All studies that reported gender were comprised of predominately male participants, except for a single study[28] with an equal number of men and women. Of the studies that reported the racial or ethnic makeup of their sample, 9 studies[7,16,17,21,25–27,32,33] were comprised predominately of Black participants, 5[8,29,30,36,41] were comprised predominately of Hispanic or Latino participants, and 14 studies[3,4,6,10,14,15,20,22,24,31,34,35,37,38] were comprised predominately of White participants. Most studies were conducted prior to the current era of increased illicit synthetic opioids and psychostimulants. Study participants mostly used IV heroin, often in combination with cocaine.

Seventeen studies provided detail about the syringe dispensation policies of the SSPs evaluated. Some of these studies evaluated multiple SSPs with different dispensation policies or SSPs whose dispensation policies changed over time and are counted more than once. Of these, 11[5,9,10,12,16,17,19,32,39,42,45] reported policies requiring exchange of a used needle for a clean needle (exchange), 7[8,14,18,19,32,34,42] reported distribution of clean syringes without requiring exchange of used needles (distribution), and 2[31,46] reported sale of up to 10 clean syringes. Of the SSPs with exchange policies, 7[5,10,12,16,17,19,45] had strict 1-for-1 exchange policies, and 4[9,32,39,42] allowed for the distribution of a small number of extra syringes (for example, as a starter pack for new SSP clients). Of the SSPs with distribution models, 2[18,32] allowed for distribution of a set number of syringes (*eg*, up to 10 per visit), while 6[8,14,18,19,34,42] distributed clean syringes based on need, without a set limit (needs-based distribution).

Sixteen studies provided information about services offered at the SSP in addition to needle exchange or distribution. Most SSPs ($N = 9$[3,8,10,14–17,20,45]) provided materials related to safer injecting practices, such as sterile injection equipment, bleach, cotton, water, and/or alcohol wipes. Eight studies[5,8,10,14,17,34,45,85] describe provision of education or educational materials on risk reduction and safer injecting practices. Three studies[10,20,34] describe provision of overdose prevention education or resources, with 2[10,34] distributing or administering naloxone. SSPs commonly provided HIV prevention

and education resources ($N = 7$[5,12,15–18,35]), as well as distribution or sale of condoms ($N = 8$[3,5,8,12,15–17,45]), and 6[14,16,17,20,34,85] offered testing for HIV and HCV. Few SSPs provided on-site medical care. One SSP[34] had co-located primary care services, while others offered basic medical care,[35,85] provided referrals for medical treatment,[8,14,16] or distributed wound care kits.[14,34] One SSP[34] had co-located drug treatment services. Eight SSPs[15–18,20,26,35,45] provided referrals to drug treatment, 2 of which[16,17] had a limited number of prepaid spots in methadone maintenance treatment available for SSP clients.

Most studies prioritized for synthesis were retrospective cohorts, pre-post, or cross-sectional. Overall, these studies are less reliable (higher risk of bias) due to selection bias and the potential for uncontrolled confounding (see Appendix for full risk of bias ratings). Other common limitations included high levels of missing data, unclear handling of missing data, and inappropriate exclusion of potential study participants. Cohort studies were also limited by unclear description of classification of the intervention. Absence of information about blinding of study personnel and deviations from the assigned intervention, as well as potential for recall bias, were limitations of included RCTs.

INJECTION FREQUENCY

SSP use does not appear to increase injection frequency among PWID. Most studies found that PWID using SSPs as a source of injection supplies may inject drugs less often over time or the same amount compared to those obtaining injection supplies from other sources (Table 2). A 2003 RCT[3] of 600 PWID in Alaska randomized to SSP access (intervention group) or training on how to purchase injection supplies from pharmacies (comparator group) found that the mean number of past 30-day injections decreased in both groups over time and was not modified by group assignment. This finding was largely supported by results of prospective cohort and pre-post studies, although in general these studies are less reliable due to risk of selection bias and confounding. In 1 pre-post study[14] in which SSP injection frequency seemed to increase over time among SSP users, a discrepancy was noted between data collected on a standard form and information obtained from private interviews, in which almost all participants reported no change in injection frequency per day. In a second study in which the percentage of participants injecting more than 5 times per day seemed to increase over time, authors did not speculate on the reasons for this finding but did note that the cohort participating in longitudinal assessments was a higher-risk group (with more reported high-risk injection behaviors) than the cohort only providing baseline data.[10]

Table 2. Injection Frequency

Study	Study Design	N	Results
Fisher 2003[3]	RCT	600	Randomization to SSP access or training on pharmacy purchase of injection supplies did not significantly modify the association between time under observation and injection.
Hagan 2000[4]	Prospective cohort	1079	Compared former, current, new, and never use of SSP controlling for drug treatment, drug usually injected, and number of injections per month at enrollment. Former exchangers were more likely to report reduced injection frequency of more than 75% compared with never exchangers (aRR = 2.85, 95% CI [1.47, 5.51]). The odds of reduced injection frequency in former exchangers vs never exchangers were greater among individuals injecting daily at enrollment (OR = 3.44, 95% CI [1.46, 8.09]). There was no significant difference between never exchangers and new or current exchangers.
Hartgers 1989[5]	Prospective cohort	54	32% of SSP users said they had injected irregularly (rather than regularly) in the last 6 mos compared with 70% of non-SSP users ($p < 0.05$).
Marmor 2000[6]	Prospective cohort	328	Mean rates of change with time in standardized drug injection rates (negative values represent a decrease in drug injection rate): SSP nonusers: -1.22, 95% CI [-1.46, -0.98]; SSP sporadic users: -0.69, 95% CI [-1.04, -0.35]; SSP consistent users: -0.41, 95% CI [-0.71, -0.10]. Injection frequency decreased in all groups, but the rate of decline was significantly less among consistent SSP users compared to non-users and sporadic users.
Monterroso 2000[7]	Prospective cohort	2306	Reduced injection frequency in participants who ever used an SSP (compared to never used SSP) OR = 0.43, 95% CI [0.31, 0.59].
Schoenbaum 1996[8]	Prospective cohort	329	Among active injectors, SSP users injecting >30 times per month 1989 to 1993: 72.6 to 49.5% ($p < 0.01$); non-exchange users change was 70.9 to 45.2% ($p < 0.001$). 43% of SSP users reduced or stopped injecting compared with 82% of non-SSP users ($p < 0.001$ for both groups).

Study	Study Design	N	Results
Bartholomew 2021[10]	Pre-post	115	Average # of injections per day among PWID who attended an SSP: baseline (n, %): <5 64 (57.7); ≥5 47 (42.3); 1st follow-up: <5 58 (53.2); ≥5 51 (46.8); 2nd follow-up: <5 47 (48.0); ≥5 51 (52.0).
Cox 2000[11]	Pre-post	370	Among PWID who attended an SSP, 70/104 (67%) who reported injecting >4 times per day reduced their injection frequency to <1 time per day ($p < 0.05$).
Donoghoe 1989[12]	Pre-post	142	Mean # of injections in the previous 4 weeks: 53 at first month of attendance vs 45 2-4 months later.
Iversen 2013[13]	Pre-post	724	Daily injection use (N, %) among PWID who attended an SSP across 3 time periods: 1995-1999: 143 (52); 2000-2003: 107 (61); 2004-2010: 110 (50) ($p = .06$).
Huo 2006[9]	Prospective cohort	707	Changes in the injection frequency of SSP users and non-users were not significantly different.
Patel 2018[14]	Pre-post	148	Among PWID who attended an SSP and completed a standardized form reporting injection behaviors, median injection times per day (IQR) first visit: 5 (3–9) compared to most recent visit 9 (5–15); $p < 0.001$. However, in private interviews, almost all participants reported no change in injection frequency per day.
Schechter 1999[15]	Pre-post	694	Among frequent SSP attendees, baseline and first follow-up visits OR injecting ≥4 times per day = 1.28, 95% CI [0.87, 1.87].
Vertefeuille 2000[16]	Pre-post	112	Among HIV-positive PWID enrolled in an SSP, past-2 weeks mean number of injections decreased 82.5 vs 60.2 ($p = .03$) at 6-month follow-up.
Vlahov 1997[17]	Pre-post	335	Mean injections per day decreased from 5.9 to 4.9 (mean change = -1.09, 95% CI [-1.50, -0.68]) at 2-week follow-up. Daily injections decreased from 5.6 to 4.1 from baseline to 6-month follow-up (mean change = -1.50, 95% CI [-2.09, -0.91], $p < .001$).
Vogt 1998[18]	Pre-post	208	Among 208 participants with repeat interviews, 100 (48%) reported a decrease in frequency of injection from the first to the most recent interview, 81 (39%) reported no change in frequency of injection, and 27 (13%) reported increase in frequency of injection.

Abbreviations. CI=confidence interval; mos=months; IQR=interquartile range; OR=odds ratio; PWID=people who inject drugs; SSP=syringe services program.

NALOXONE DISTRIBUTION AND OVERDOSE EDUCATION

PWID who have used an SSP are more likely to have received naloxone or say that they are carrying naloxone compared to those who have not used an SSP based on consistent, statistically significant results from 4 cross-sectional studies,[20–23] (Table 3). Receiving overdose education was less frequently studied, but also appears to be positively associated with SSP use based on results from 2 cross-sectional studies.[21,24] A small cross-sectional study[21] of 263 PWID in Philadelphia examined naloxone possession and receipt of overdose education according to SSP use and race and found that Black and White SSP clients were both more likely than Black non-SSP clients to possess naloxone and receive overdose training.

Table 3. Naloxone Distribution and Overdose Education

Study	Study Design	N	Results
Naloxone Distribution			
Allen 2021[20]	Cross-sectional	420	Having accessed sterile syringes at an SSP: aPR[a] received naloxone in the past 6 mos = 1.36; 95% CI [1.18, 1.57].
Jones 2021[21]	Cross-sectional	263	Black SSP clients (aOR[b] = 4.21, 95% CI [2.0, 8.87]), White SSP clients (aOR[b] = 3.54, 95% CI [1.56, 8.04]), and White non-SSP clients (aOR[b] = 4.49, 95% CI [1.5, 13.37]) were more likely to possess naloxone compared to Black non-SSP clients.
Reed 2019[22]	Cross-sectional	571	SSP as primary source for syringes in the past 12 mos compared to a pharmacy or secondary source (friend, relative, sex partner, dealer, shooting gallery, or off the streets): aOR[c] carrying naloxone = 2.92, 95% CI [1.68, 5.09].
Spring 2022[23]	Cross-sectional	2,139	Past-year contact with SSP: aOR[d] carrying naloxone = 1.74, 95% CI [1.39, 2.18].
Turner-Bicknell 2020[19]	Serial cross-sectional	NR	Naloxone distribution increased from 29 kits prior to SSP implementation (July 2017) to 88 kits in September 2017 (post-implementation) but decreased to 69 in December 2017).
Overdose Education			
Jones 2021[21]	Cross-sectional	263	Black SSP clients (aOR[b] = 3.85, 95% CI [1.88, 7.92]) and White SSP clients (aOR[b] = 2.73 95% CI [1.29, 5.75]) (but not White non-SSP clients aOR[b] = 0.54 [0.19, 1.55]) were more likely to have received overdose training compared to Black non-SSP clients.
Kim 2021[24]	Cross-sectional	458	Accessed an SSP: aOR[e] received overdose training = 3.51, 95% CI [1.41, 8.79].

Notes. [a] Adjusted for age, single status, food insecurity, injection drug use past 6 mos, prescription opioid pain relievers, heroin, fentanyl, receptive syringe sharing past 6 months. [b] Adjusted for sociodemographic and drug use variables. [c] Adjusted for homeless status and law enforcement interactions. [d] Adjusted for region of recruitment, gender, born in UK, injecting duration, ever engaged in transactional sex, currently homeless, been in prison in the past year, prescribed treatment for drug use, heroin use and use of other central nervous system depressants in the past month, overdosed in the past year. [e] Adjusted for demographic factors, homeless in the last 12 months, experience of overdose, witnessed overdose in last 12 months, currently own naloxone, drug most frequently injected, and frequency of injection.

Abbreviations. aOR=adjusted odds ratio; aPR=adjusted prevalence ratio; mos=months; NR=not reported; SSP=syringe services program.

LINKAGE TO SUD TREATMENT AND UTILIZATION OF TREATMENT SERVICES

SSP use may be associated with increased treatment linkage and/or use of treatment services among PWID compared to no SSP use (or less use) (Table 4). The most recent and direct evidence is from a 2006 retrospective cohort study[25] of 440 PWID in Baltimore which found that after adjusting for gender, employment status, type and method of drugs used, and HIV status, individuals who used an SSP in the past 6 months were more likely than those who did not to enter drug treatment, which was broadly defined to include drug detoxification, residential treatment, methadone maintenance, and outpatient drug-free treatment (aOR = 1.71, 95% CI [1.12, 2.62]). Similarly, an earlier cohort study[86] also conducted in Baltimore found that HIV-negative PWID who used an SSP were more likely to enter methadone treatment in the subsequent 6 months than those who had not used an SSP, particularly early in the study period when the SSP was able to offer dedicated treatment slots for its

clients (OR 1994-1995 = 1.9, 95% CI [1.34, 2.62]; OR for the study period = 1.48, 95% CI [1.13, 1.75]). In this cohort, SSP attendance was also associated with entry into a medically supervised withdrawal facility for both HIV-positive (aOR = 3.2, 95% CI [1.38, 7.53]) and HIV-negative individuals (aOR = 1.38, 95% CI [1.02, 1.87]).[27]

Two cohorts evaluated treatment retention among those referred to treatment from an SSP compared to another source. In a cohort study[28,87] of 325 PWID in Baltimore, 6- and 12-month treatment retention was no different for those referred by the SSP compared to those referred by other means (self-referral, family referral, other healthcare provider referral, *etc*) after adjusting for demographic variables, employment status, and days of heroin, cocaine, and IDU in the month prior (6 months aHR = 1.39, 95% CI [0.61, 2.04]; 12 months aHR = 1.23 95% CI [0.78, 1.94]). In another cohort study[4] conducted in Seattle, those who stopped attending the SSP during the 12-month study period were more likely to continue methadone treatment compared to those who never used the SSP (aRR = 1.55, 95% CI [0.90, 2.68]), although this finding was not statistically significant. Retention in methadone treatment was similar for current SSP users or those who started using the SSP during the study period compared to those who never used the SSP.

Table 4. Linkage to SUD Treatment and Utilization of Treatment Services

Study	Study Design	N	Results
Initiated Treatment			
Hagan 2000[4]	Cohort	Variable	Participants who started attending the SSP during the 12-month study period (new SSP users) were more likely to enter a methadone program (aRR = 5.05, 95% CI [1.44, 17.7])[a] compared with those who formerly, currently, or never used the SSP.
Hartgers 1989[5]	Cohort	145	At baseline, individuals using an SSP > 90% of the time in the last 6 mos had been in contact with methadone programs more often in the last 5 years than less frequent or non-SSP users (76% vs 48%, $p < 0.01$).
Latkin 2006[25]	Cohort	440	Individuals who utilized an SSP in the past 6 mos were more likely to have entered drug treatment than individuals without past 6-mos SSP use (aOR = 1.71, 95% CI [1.12, 2.62]).[b]
Kuo 2003[26]	Cohort	163	70% of SSP users referred for drug treatment using LAAM (an opioid agonist no longer on the US market) enrolled in the program (114 vs 41). Treatment entry did not differ according to the number of SSP visits prior to accepting the referral.
Strathdee 1999;[27]Shah 2000[86]	Cohort	1,483	HIV-negative participants who attended the SSP were more likely to enroll in methadone maintenance in the subsequent 6 mos compared to those who did not attend the SSP (aOR = 1.48, 95% CI [1.13, 1.75]).[c] SSP attendance was associated with entry into a medically supervised withdrawal facility for both HIV-positive (aOR = 3.2, 95% CI [1.38, 7.53])[d] and HIV-negative individuals (aOR = 1.38, 95% CI [1.02, 1.87]).[b]
Cox 2000[11]	Pre-post	370	There was a nonsignificant increase in the percentage of participants attending other drug treatment services at 3-month follow-up (26% at follow-up vs 20% at baseline, $p < 0.075$).
Vertefeuille 2000[16]	Pre-post	112	Participation in SUD treatment increased between baseline and 6-month follow up in HIV-seropositive SSP participants (8% vs 18.8%, $p = 0.01$).

Study	Study Design	N	Results
Vlahov 1997[17]	Pre-post	335	Self-reported engagement in treatment increased from 6.3% at baseline to 9.0% at 2-week follow-up (p = .117).
Retained in Treatment			
Brooner 1998;[28]Neufeld 2008[87]	Cohort	325	6- and 12-month treatment retention was no different for those referred by the SSP compared to those referred by other means (self-referral, family referral, other health care provider referral, *etc*) after adjusting for baseline variables (6 mos Ahr = 1.39, 95% CI [0.61, 2.04]; 12 mos aHR = 1.23, 95% CI [0.78, 1.94]).[e]
Hagan 2000[4]	Cohort	Variable	Former SSP users who stopped attending the SSP during the 12-month study period were more likely to remain in methadone treatment at 12-month follow up compared to those who never used the SSP (aRR 1.55, 95% CI [0.90, 2.68]).[f] Retention in methadone treatment was similar for current SSP users or those who started using the SSP during the study period compared to those who never used the SSP.

Notes. [a] Adjusted for gender; [b] Variables controlled for in adjusted analysis not reported; [c] Adjusted for gender, employment status, sniff/snort cocaine, sniff/snort heroin, history of mental illness, HIV positive status; [d] Adjusted for interaction between lagged SSP attendance and calendar year; [e] Adjusted for demographic variables, employment status, and days of heroin, cocaine, and IDU in the prior month; [f] Adjusted for frequency of injection at study enrollment.

Abbreviations. AE=adverse events; aOR=adjusted odds ratio; aPR=adjusted prevalence ratio; aRR=adjusted risk ratio; HIV=human immunodeficiency virus; HR=hazard ratio; IVDU=intravenous drug use; LAAM=levomethadyl acetate hydrochloride; mos=months; NR=not reported; PWID=people who inject drugs; RCT=randomized controlled trial; SSP=syringe services program; SUD=substance use disorder.

SYRINGE DISPOSAL

SSP use and/or presence of an SSP does not appear to increase unsafe syringe disposal practices based on 1 RCT, 2 pre-post studies, 11 cross-sectional studies, and 7 ecological studies (3 of which also included cross-sectional data) evaluating whether SSP use or presence of an SSP within a community was associated with safe (*eg*, return to SSP) or unsafe (*eg*, dispose in trash or leave on street) methods of syringe disposal (Table 5). Three cross-sectional studies[33,38,39] with a combined sample of more than 1,500 participants in large cities (Baltimore, New York City, San Francisco, and Vancouver, BC) found that safe syringe disposal was 2.28 to 5.79 times more likely among those who used an SSP compared to those who did not.

Table 5. Syringe Disposal

Study	Study Design	N	Results
Lewis 2015[29]	Cluster RCT	482	Safe syringe disposal (N, %) among PWID receiving supplies at control group pharmacies: 96 (39.5) at baseline and 91 (46.4) at 3 mos, p = .1263; Safe syringe disposal (N, %) among PWID receiving supplies at intervention group pharmacies: 74 (33.5) at baseline and 72 (42.1) at 3 mos, p = .040; between-group differences non-significant.
Vertefeuille 2000[16]	Pre-post	112	Baseline and 6 mos proportion of participants discarding of syringes in the garbage (48.6% vs 37.8%, p = .13) and in the street (7.5% vs 2.5%, p = .32).

Study	Study Design	N	Results
Vlahov 1997[17]	Pre-post	335	Proportion of participants who discarded needles in a street, alley, sewer, or gutter (28.2% vs 15.6%; $p < .001$) and in the garbage or a dumpster (42.4% vs 29.1%; $p < .001$) before and after enrolling in SSP.
Cleland 2007[30]	Serial cross-sectional	1030	Syringes obtained from an SSP were more likely to be disposed of safely than syringes from other sources: SSP syringe source vs other aOR safe vs unsafe disposal = 22.39, 95% CI [12.93, 38.78]; SSP syringe source vs other aOR safe vs possibly safe disposal = 20.98, 95% CI [12.95, 33.99].[a]
Cotten-Oldenburg 2001[31]	Serial cross-sectional	566	Pre/post legislation allowing for voluntary pharmacy sales of syringes/needles without a prescription for an accompanying drug; safe syringe disposal aOR = 1.32,[b] 95% CI [0.84, 2.06].
Bluthenthal 2004[32]	Cross-sectional	584	PWID received syringes from SSP within 30 days ($N = 155$)[c]: return to SSP: 85.2%; trash: 20.6%; leave at place of injection: 2.6%; flush down toilet: 1.9%; PWID with no direct receipt of syringes from SSP within 30 days ($N = 412$)[c]: return to SSP: 6.1%; trash: 70.6%; leave at place of injection: 7.3%; flush down toilet: 4.4%.
Coffin 2007[33]	Cross-sectional	680	Ever been to SSP compared to never used SSP: aOR safe syringe disposal = 5.79, 95% CI [3.13, 10.69].
Dasgupta 2019[34]	Cross-sectional	200	Among those injecting drugs before and after the public health response[d] ($N = 124$), disposal of used syringes in a designated medical waste container increased from 17% to 82%.
Khoshnood 2000[35]	Cross-sectional	373	Compared to pharmacy as the usual source of syringes, SSP source: OR threw away syringe "sometimes to always" = 0.03, 95% CI [0.006, 0.15]; both SSP and pharmacy source: OR threw away syringe "sometimes to always" = 0.11, 95% CI [0.02, 0.51]; source other than SSP or pharmacy: OR threw away syringe "sometimes to always" = 0.29, 95% CI [0.02, 3.5].
Quinn 2014[36]	Cross-sectional	412	SSP main syringe source aOR[e] improper disposal last 30 days = 0.44, 95% CI [0.26, 0.75]; aOR[f] improperly disposed of >50% total syringes disposed last 30 days = 0.19, 95% CI [0.10, 0.36].
Riley 2010[37]	Cross-sectional	105	Obtaining syringes from an SSP aOR[g] unsafe disposal = 0.17, 95% CI [0.05, 0.95].
Sherman 2004[38]	Cross-sectional	294	Safe syringe acquisition (SSP or pharmacy) aOR[h] safely disposing syringes = 2.28, 95% CI [1.20, 4.37].
Wood 2003[39]	Cross-sectional	587	Use of an all-night SSP compared to other sources (including fixed SSP) aOR[i] safer syringe disposal = 2.69; 95% CI [1.38, 5.21].
Zlotorzynska 2018[40]	Cross-sectional	6321	Obtaining syringes primarily from pharmacies vs SSPs: aOR[j] any unsafe syringe disposal = 1.47, 95% CI [1.38, 1.56].
Levine 2019[41]	Ecological and serial cross-sectional	930, 775 census blocks	Total 371 syringes/1,000 blocks found pre-SSP implementation compared to 191 syringes/1,000 blocks found post-SSP implementation (49% decrease); improper syringe disposal post-SSP implementation compared to pre-implementation aRR = 0.61,[k] 95% CI [0.55, 0.69].
Tookes 2012[42]	Ecological and serial cross-sectional	1050	Miami (city without SSP) syringe density = 371/1000 census blocks and syringe prevalence = 4.9/1000 people; San Francisco (city with SSP) syringe density = 44/1000 census blocks and syringe prevalence = 0.3/1000 people; Miami compared to San

Study	Study Design	N	Results
			Francisco: aOR[l] public syringe disposal = 34.2, 95% CI [21.9, 53.5].
Wenger 2011[m43]	Ecological and cross-sectional	602	Obtained syringes from SSP compared to other source: aOR[g] improper syringe disposal = 0.20; 95% CI [0.10, 0.40].
Broadhead 1999[44]	Ecological	1 town	From fall 1996 to fall 1997 (following SSP closure), the rate of discarded syringes increased from 26.1 per month 39.8 per month (53% increase).
Doherty 1997[45] Doherty 2000[88]	Ecological	32 city blocks	Block mean of number of needles per 100 trash items was 2.42 pre-SSP and 1.30 2 years post-SSP (mean within-block change = −0.028, $p < .05$).
Fuller 2002[46]	Ecological	27 blocks	Decrease in block mean ratios of syringe to background trash pre-SSP (1.17 and 1.03) compared with post-SSP (0.81, 0.53, 0.73).[n]
Oliver 1992[47]	Ecological	1 neighbor-hood	5.14 syringes found per month pre-SSP implementation compared with 1.9 post-SSP implementation, $p < .05$.

Notes. [a] Safe methods of disposal included clinic, doctor, hospital, SSP, pharmacy, disposal mailbox, and sharps box. Unsafe methods of disposal included bushes, toilet, sewer, stranger, ground, owner, and left. Possibly safe methods of disposal included garbage at home and garbage elsewhere; [b] Adjusted for speedball injection and prison history; [c] ESP calculated; [d] The public health response included establishment of the state's first legal SSP (other components of the public health response were not described);[e] Controlled for recruitment site; [f] Controlled for income; [g] Variables controlled for in adjusted analysis not reported; [h] Controlling for ethnicity, gender, education level, and age; [i] Adjusted for age, HIV positivity, unstable housing, residence in the HIV epicentre, involvement in the sex trade, frequency of heroin use, reuse of syringes, and injecting alone; [j] Adjusted for age, race/ethnicity, gender, education, current homelessness, self-reported HIV status and injection frequency; [k] Adjusting for gender, age, race/ethnicity, homelessness, and HIV-positive status; [l] Adjusting for age, gender, homelessness, and self-reported HIV seropositivity; [m] Sample includes San Francisco participants from Tookes 2012 study; [n] Counts were made at 2 time points prior to SSP (October 25, 2000 and January 30, 2001) and 3 time points following SSP (April 25, 2001, June 27, 2001, and December 5, 2001).

Abbreviations. AOR=adjusted odds ratio; ARR=adjusted risk ratio; CI=confidence interval; mos=months; OR=odds ratio; PWID=people who inject drugs; SSP=syringe services program.

NEIGHBORHOOD CRIME RATES

Presence of an SSP may not be associated with any change in neighborhood crime rates. We identified 2 ecological studies[48,49] measuring community crime rates based on proximity to an SSP or pharmacy selling syringes (Table 6). While a study in New York City found that SSP access was associated with increased arrests, a study in Baltimore evaluating the same outcome found no difference in arrest trends. Neither study controlled for other variables that could account for local arrest trends, but the study conducted in Baltimore likely provides more reliable information because it more directly measured arrest trends relative to the start of an SSP.

Table 6. Neighborhood Crime Rates

Study	Study Design	N	Results
Cooper 2012[48]	Ecological	42 health districts in New York City	On average a 1-unit increase in logged SSP access over time was associated with an increase of 11.18 arrests/1000 residents ($p < 0.0001$).
Marx 2000[49]	Ecological	Baltimore areas within 0.5-mile radius of an SSP site	No significant differences in arrest trends by category after SSP introduction relative to before SSP introduction in program vs non-program areas ($p > .05$)

Abbreviations. SSP=syringe services program.

SSP DISTRIBUTION MODELS

Use of SSPs that offer more syringes per visit or supply syringes based on need (regardless of how many used syringes are returned) may be associated with less syringe re-use compared to use of SSPs with more restrictive syringe distribution policies, such as caps on the number of syringes that may be supplied per visit or requirements for 1-for-1 syringe exchange (*ie*, 1 sterile syringe is supplied for every used syringe that is returned) (Table 7). A 2010 systematic review[2] of SSP effectiveness included 3 cross-sectional studies[32,89,90] evaluating SSPs according to syringe distribution policies. Two of these cross-sectional studies[32,89] compared injection risk behaviors among PWID using SSPs or pharmacies with variable syringe dispensation policies and/or limits on the number of syringes that could be supplied. A third cross-sectional study[90] compared injection risk behaviors among PWID in Hartford, CT when the number of syringes permitted to be dispensed by SSPs increased from 5 to 10. Results were consistent across studies showing that use of SSPs with more permissive syringe distribution practices (*eg*, needs-based) was associated with less reported syringe re-use. No differences were found for reports of syringe sharing in 2 studies.

Table 7. SSP Exchange Models

Syringe Policy	Evidence	Findings
Needs based or >1 for 1 exchange vs 1-for-1 exchange	1 SR[2] (2 cross-sectional studies[32,89])	Syringe re-use: Less syringe re-use with needs-based or >1 for 1 syringe access compared to 1-for-1 or limited syringe exchange[32,89] Syringe sharing: No difference in receptive syringe sharing according to SSP syringe exchange policies[32,89]
Increase in the number of syringes dispensed from 5 to 10	1 SR[2] (1 cross-sectional study[90])	Mean percent of injections using a pre-used syringe decreased from 14% to 11% when syringe distribution cap increased from 5 to 10

Abbreviations. SR=systematic review; SSP=syringe services program.

SSP PROGRAM COMPONENTS

Combined SSP and OUD Treatment Programs

The 2022 review of reviews[1] on HIV/HCV transmission and injection risk behaviors evaluated evidence on combined SSPs and OUD treatment programs, finding that while evidence was insufficient for the outcome of HIV transmission (no studies were identified), sufficient evidence existed regarding a benefit of combined programs on reducing HCV transmission. This conclusion was

largely based on a systematic review and meta-analysis, Platt et al,[81] of 3 types of studies, which found that use of an SSP combined with opioid agonist therapy resulted in a significantly lower risk of HCV transmission (RR = 0.26, 95% [CI 0.07, 0.89], with a larger effect size than was seen for SSP use or opioid agonist therapy alone. This finding was consistent with another meta-analysis[91] of 2 cohorts and 4 cross-sectional studies included in the original 2010 review of reviews.[78] That meta-analysis also reported that combined SSP and opioid agonist therapy was associated with 48% reduction in odds of self-reported needle sharing (aOR = 0.52, 95% CI [0.32, 0.83]).

Additional Harm Reduction and Referral Services

Whether motivational interviewing or strengths-based case management improves treatment enrollment among PWID using an SSP is unclear (Table 8). A trial[92] of a motivational interviewing intervention among PWID accessing a SSP in Baltimore found no difference in treatment entry. Findings were mixed with regard to strengths-based case management, with 1 trial[93] conducted among PWID using an SSP in Baltimore finding that case management after treatment referral resulted in greater treatment entry (OR = 1.84, 95% CI [1.07, 3.16]), and another trial of a similar case management intervention among PWID in Sweden with high enrollment rates overall finding no effect.[85] In the Baltimore trial, intention-to-treat analysis controlling for distance to travel, access to care, and clustering by SSP site did not show a difference in treatment enrollment between intervention and control groups, leading authors to conclude that benefits of case management could be attributed to the provision of transportation.

Whether harm reduction education and referral to services offered by staff at a pharmacy-based SSP improves injection risk behaviors, safe syringe disposal, or treatment uptake is also unclear (Table 8). In a trial[29] conducted in New York City in which pharmacies were randomized to offer harm reduction services or usual care, no benefit was seen among PWID using intervention group pharmacies in regard to injection frequency, syringe sharing, safe syringe disposal, or receipt of detoxification or drug treatment.

Table 8. Additional Harm Reduction Services[a]

SSP Approaches	Evidence	Findings
Motivational interviewing	1 SR[2] (1 RCT[92])	Treatment enrollment: No difference in treatment entry with a motivational interviewing intervention
Strength-based case management services	1 SR[2] (1 RCT[93]), 1 RCT[85]	Treatment enrollment: A strength-based case management intervention delivered after treatment referral resulted in greater treatment entry,[93] while a similar intervention delivered prior to treatment referral did not result in greater treatment enrollment among a population with high enrollment rates overall (95% in the intervention group and 94% in the control group)[85]
Harm reduction education and referral to services	1 RCT[29]	No difference in injection frequency, syringe sharing, safe syringe disposal, or receipt of detoxification or drug treatment between pharmacy-based SSPs randomized to offer harm reduction services[b] compared to usual care

Notes. [a] Two RCTs were included in the Jones 2010 SR and 2 were published after this review and were included as primary studies in our review; [b] HIV prevention/medical/social service referrals, syringe disposal containers, and harm reduction print materials.

Abbreviations. HIV=human immunodeficiency virus; RCT=randomized controlled trial; SR=systematic review; SSP=syringe services program.

DISCUSSION

This review aimed to integrate a large and complex evidence base on the effectiveness and potential harms of SSPs to inform VHA policies and program development. Reducing harms due to substance use is a goal of the Office of National Drug Control Policy,[71] as well as VA Offices of Mental Health and Suicide Prevention, Research and Development, and Specialty Care Services.

Findings of this review are based on more than 4 decades of research on SSPs. Despite broad changes in drug use patterns and shifts in policies related to how SSPs are permitted to operate, findings regarding the effectiveness of SSPs have been largely consistent over time. A 2022 review of reviews[1] found sufficient evidence that SSPs prevent HIV transmission among PWID and tentative evidence that SSPs prevent HCV transmission. Studies of HCV prevention had less consistent results compared to studies of HIV prevention, but it is unknown whether the weaker benefit in terms of HCV prevention is primarily due to study factors (such as the ways SSP use was defined and measured in studies evaluating HCV transmission) or differences in HIV and HCV transmissibility. Additionally, the relatively recent availability of curative therapy options for HCV is likely altering the epidemiology of HCV in ways that have not yet been reflected in available evidence. Combined SSP and opioid agonist treatment may improve HCV prevention to a greater degree than either intervention alone.

The same 2022 review of reviews[1] found sufficient evidence that SSP use reduced injection risk behaviors, an important intermediate outcome when considering that a primary aim of SSPs is to prevent infectious disease transmission. SSP use may also be associated with increased treatment linkage and/or use of treatment services among PWID compared to no SSP use (or less use).

SSP use does not appear to increase injection frequency among PWID, result in an increase in unsafe syringe disposal practices, or directly increase neighborhood crime rates. Authors of a 2012 ecological study[48] of arrest trends in proximity to SSP locations in New York City noted "the spatial overlap of these two features of the risk and protective environment likely reflects their shared target population and target behaviors." This framing underscores the point noted by several study authors that SSPs serve a segment of the PWID population with a higher baseline risk for drug-related harms, including legal system involvement. Despite this higher baseline risk, we found no evidence that SSP use further heightens risk to PWID or communities.

Studies of public health interventions in real-world settings often must rely on observational research methods that are intrinsically less rigorous than study designs available in clinical contexts. These methodological limitations lower the strength of available evidence for individual SSP outcomes (see Appendix). However, when looking across outcomes, the preponderance of evidence demonstrating the potential benefits of SSPs and relative lack of harms is more than sufficient to support SSP implementation when possible. This overall conclusion is consistent with recommendations from several public health organizations and professional societies regarding the role of SSPs in harm reduction, including statements from the CDC describing SSPs as "safe, effective, and cost-saving" (see Table 9).

Table 9. Public Health Organization and Professional Society Statements Regarding SSPs

American Academy of Addiction Psychiatry[94]	Supports the funding and development of programs that assist people, who are injecting drug users, to have increased access to clean needles and syringes to help them eliminate all reusing and sharing of needle syringes.
American Bar Association[95]	Expressed support in 2011 for continuation of federal funding for syringe exchange programs, which the association maintains are an effective public strategy for reducing the transmission of HIV/AIDS in the United States.
American Medical Association[96]	The AMA strongly supports needle and syringe exchange programs as part of a wider harm reduction approach to treating substance abuse and addiction.
American Public Health Association[97]	State and local health departments, tribal leaders and/or councils, and community agencies should implement comprehensive SSPs for people who inject drugs to mitigate the risk of blood-borne infections (HIV and HCV) at the community level.
Centers for Disease Control and Prevention[98,99]	Nearly 30 years of research shows that comprehensive SSPs are safe, effective, and cost-saving, do not increase illegal drug use or crime, and play an important role in reducing the transmission of viral hepatitis, HIV, and other infections.
European Centre for Disease Prevention and Control and European Monitoring Centre for Drugs and Drug Addiction[100]	2011 guidance states that provision of, and legal access to, clean drug injection equipment, including sufficient supply of sterile needles and syringes, free of charge, as part of a combined multi-component approach implemented through harm-reduction, counseling, and treatment programs, is a key intervention component for prevention of infections among PWID.
Joint United Nations Progamme on HIV/AIDS (UNAIDS)[101]	Given the prominence of unsafe injecting drug use due to the limited availability of needle and syringe programs in the HIV epidemics in many countries, comprehensive harm reduction services are vitally important, including in prisons and other closed settings. The services therefore should include needle and syringe programs, opioid substitution therapy and naloxone, and should address the specific needs of women who use drugs.
World Health Organization[102]	Evidence from 20 years of research shows that needle and syringe programs prevent, control, and ultimately reduce prevalence of HIV and other blood-borne infections among injecting drug users.

Abbreviations. AMA=American Medical Association; HCV=hepatitis C virus; HIV=human immunodeficiency virus; PWID=people who inject drugs; SSP=syringe services program.

Limitations

The existing evidence base has several limitations. First, studies used different measures for SSP exposure (*eg*, number of visits, percent of syringe coverage, *etc*) and outcomes, limiting our ability to compare results across studies in some cases. Second, many studies relied on participant self-report for both SSP use and outcomes of interest. In general, participant self-report has potential for recall bias and social desirability bias. Third, observational studies have potential bias due to uncontrolled confounding. While several studies used adjusted analyses to minimize the effect of confounding variables, effect estimates could still be skewed by unmeasured confounders. Finally, even though study periods span 4 decades, most studies were conducted in urban populations and prior to the current era of substance use in which illicit fentanyl and methamphetamine use is more common.

Although most findings discussed in this review are broadly applicable to a range of populations and settings, whether specific benefits of SSPs apply to all segments of PWID is unclear.

FUTURE RESEARCH

Despite some evidence gaps, additional research on existing SSP models may not be of practical value to health care policymakers given that available evidence is sufficient to support SSP implementation when possible. However, given that drug use patterns are constantly evolving and often regionally specific, future research on strategies to improve the responsiveness of SSPs to shifts in drug use patterns would be informative. For example, studies included in this review were largely conducted prior to the emergence of xylazine as a more common component of the illicit drug supply.[103] Future research could examine best practices to provide PWID with tools and information needed to reduce harms associated with xylazine exposure.

We note that studying SSPs presents several methodological challenges. One challenge is how to compare findings across SSPs, which may have inconsistent approaches to defining and measuring outcomes.[104] Another challenge is integrating data sources to derive valid and meaningful conclusions. A recent study using administrative data to evaluate links between SSPs openings and drug-related health outcomes illustrates this point.[105] In this study, the author concluded that SSPs increase rates of opioid-related mortality based on an analysis of county-level data on SSP openings and overdose fatalities. However, this analysis has been criticized for assuming that because an association exists between an exposure and an outcome at the population level, it exists at the individual level (a concept known as ecological fallacy).[106] Future researchers have the benefit of learning from decades of research on SSPs and should take care to avoid known causes of data misinterpretation.

CONCLUSIONS

SSP utilization likely results in lower HIV transmission and reduced injection risk behaviors, and may result in lower HCV transmission, promote carrying naloxone, increase exposure to overdose education, and facilitate referral to and enrollment in treatment services. SSP use and presence in communities does not appear to increase injection frequency, unsafe syringe disposal practices, or neighborhood crime rates. Combined SSP and opioid agonist treatment may improve HCV prevention to a greater degree than either intervention alone. The effectiveness of other SSP program components or practices has been less frequently studied and evidence is insufficient to draw conclusions regarding best practices. Overall, when viewed as a harm reduction intervention, SSPs appear to offer a range of potential benefits without evidence suggesting that SSPs introduce harms or other unintended consequences.

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Appendix

SEARCH STRATEGIES

Search Date: 03/01/23		Search Statement	Results
Ovid MEDLINE	1	Needle-Exchange Programs/ or (((needle* or syringe*) adj2 (exchange* or program* or service*)).ti,ab,kf.	3566
	2	limit 1 to English language	3342
CINAHL	1	(MH "Needle Exchange Programs") OR TI (((needle* OR syringe*) N2 (exchange* OR program* OR service*)))	2175
	2	limit 1 to English language	2162
PsycINFO	1	Needle Exchange Programs/ or ((needle* or syringe*) adj2 (exchange* or program* or service*)).ti,ab.	1506
	2	limit 1 to English language	1430
Cochrane Database of Systematic Reviews	1	MeSH descriptor: [Needle-Exchange Programs] this term only	44
	2	(((needle* or syringe*) NEAR/2 (exchange* or program* or service*)) or (supervis* NEAR/2 injecti* NEAR/2 (center* or centre* or facilit*))):ti,ab,kw	195
	3	limit 3 to reviews	2
	4	limit 4 to english language	2
	5	limit 5 to last 7 years	2
		Total	6,936
		Total after deduplication	3,743

STUDIES EXCLUDED DURING FULL-TEXT SCREENING

Citation	Exclude Reason
Aalto M, Visapaa J-P, Halme JT, Fabritius C, Salaspuro M. Effectiveness of buprenorphine maintenance treatment as compared to a syringe exchange program among buprenorphine misusing opioid-dependent patients. Nordic Journal of Psychiatry. 2011;65(4):238-243.	Ineligible outcome
Abou-Saleh MT, Foley S. Prevalence and incidence of hepatitis C in drug users: A review. Addictive Disorders & Their Treatment. 2008;7(4):190-198.	Ineligible publication type
Adams M, An Q, Broz D, Burnett J, Wejnert C, Paz-Bailey G. Distributive syringe sharing and use of syringe services programs (SSPs) among persons who inject drugs. AIDS and Behavior. 2019;23(12):3306-3314.	Ineligible study design
Aitken CK, Kerger M, Crofts N. Peer-delivered hepatitis C testing and counselling: A means of improving the health of injecting drug users. Drug and Alcohol Review. 2002;21(1):33-37.	Ineligible study design
Alanko Blome M, Bjorkman P, Flamholc L, Jacobsson H, Widell A. Vaccination against hepatitis B virus among people who inject drugs - A 20year experience from a Swedish needle exchange program. Vaccine. 2017;35(1):84-90.	Ineligible outcome
Allen EJ, Palmateer NE, Hutchinson SJ, Cameron S, Goldberg DJ, Taylor A. Association between harm reduction intervention uptake and recent hepatitis C infection among people who inject drugs attending sites that provide sterile injecting equipment in Scotland. International Journal of Drug Policy. 2012;23(5):346-352.	Ineligible study design
Allen ST, Grieb SM, O'Rourke A, et al. Understanding the public health consequences of suspending a rural syringe services program: A qualitative study of the experiences of people who inject drugs. Harm Reduction Journal. 2019;16.	Ineligible comparator
Allen ST, Schneider KE, Mazhnaya A, et al. Factors Associated with Likelihood of Initiating Others into Injection Drug Use Among People Who Inject Drugs in West Virginia. AIDS and behavior. 2022;26(1):47-56.	Ineligible outcome
Alpren C, Dawson EL, John B, et al. Opioid Use Fueling HIV Transmission in an Urban Setting: An Outbreak of HIV Infection Among People Who Inject Drugs-Massachusetts, 2015-2018. American journal of public health. 2020;110(1):37-44.	Ineligible study design
Amundsen EJ, Eskild A, Stigum H, Smith E, Aalen OO. Legal access to needles and syringes/needle exchange programmes versus HIV counselling and testing to prevent transmission of HIV among intravenous drug users: A comparative study of Denmark, Norway and Sweden. European Journal of Public Health. 2003;13(3):252-258.	Ineligible study design
Andia JF, Deren S, Robles RR, Kang S-Y, Colon HM. Peer norms and sharing of injection paraphernalia among Puerto Rican injection drug users in New York and Puerto Rico. AIDS Education and Prevention. 2008;20(3):249-257.	Ineligible study design
Anonymous. Drug abuse. Study says clean drug needles cut HIV infections in half. AIDS policy & law. 1994;9(23):1-7.	Unable to locate FT
Anonymous. Needle exchange ends HIV transmission in Swiss jail. AIDS policy & law. 1996;11(13):9.	Ineligible publication type
Anonymous. Update: syringe exchange programs--United States, 1997. MMWR Morbidity and mortality weekly report. 1998;47(31):652-655.	Ineligible outcome
Anonymous. Update: syringe exchange programs--United States, 2002. MMWR Morbidity and mortality weekly report. 2005;54(27):673-676.	Ineligible comparator
Azores-Gococo NM, Fridberg DJ. Harm-reduction strategies for injection drug use. Psychiatric Annals. 2017;47(1):45-48.	Ineligible publication type

Citation	Exclude Reason
Bartholomew TS, Tookes HE, Serota DP, Behrends CN, Forrest DW, Feaster DJ. Impact of routine opt-out HIV/HCV screening on testing uptake at a syringe services program: An interrupted time series analysis. The International journal on drug policy. 2020;84:102875.	Ineligible outcome
Bayani A, Ghiasvand H, Rezaei O, et al. Factors associated with HIV testing among people who inject drugs: a meta-analysis. Journal of addictive diseases. 2020;38(3):361-374.	Ineligible outcome
Behrends CN. Evaluating the impact of satellite syringe exchange on reducing hiv risk behavior and seroconversion among people who inject drugs. Dissertation Abstracts International: Section B: The Sciences and Engineering. 2016;76(7-B(E)):No-Specified.	Ineligible intervention
Behrends CN, Li C-S, Gibson DR. Decreased odds of injection risk behavior associated with direct versus indirect use of syringe exchange: Evidence from two California cities. Substance Use & Misuse. 2017;52(9):1145-1153.	Ineligible study design
Behrends CN, Nugent AV, Des Jarlais DC, Frimpong JA, Perlman DC, Schackman BR. Availability of HIV and HCV On-Site Testing and Treatment at Syringe Service Programs in the United States. Journal of acquired immune deficiency syndromes (1999). 2018;79(2):e76-e78.	Ineligible outcome
Belisle LA, Solano-Patricio EDC. Harm reduction: a public health approach to prison drug use. International journal of prisoner health. 2021;ahead-of-print(ahead-of-print).	Ineligible publication type
Benninghoff F, Morency P, Geense R, Huissoud T, Dubois-Arber F. Health trends among drug users attending needle exchange programmes in Switzerland (1994-2000). AIDS Care. 2006;18(4):371-375.	Ineligible comparator
Betteridge G. Germany: study shows effectiveness of prison needle exchange. HIV/AIDS policy & law review. 2006;11(1):33-36.	Ineligible publication type
Bhattacharya MK, Naik TN, Palit A, Bhattacharya SK. Impact of a harm-reduction programme on soft tissue infections among injecting drug users of Kolkata, India. Journal of health, population, and nutrition. 2006;24(1):121-122.	Ineligible outcome
Birkhead GS, Klein SJ, Candelas AR, et al. Integrating multiple programme and policy approaches to hepatitis C prevention and care for injection drug users: A comprehensive approach. International Journal of Drug Policy. 2007;18(5):417-425.	Ineligible publication type
Blome MA, Bjorkman P, Flamholc L, Jacobsson H, Molnegren V, Widell A. Minimal transmission of HIV despite persistently high transmission of hepatitis C virus in a Swedish needle exchange program. Journal of viral hepatitis. 2011;18(12):831-839.	Ineligible study design
Bluthenthal RN, Gogineni A, Longshore D, Stein M. Factors associated with readiness to change drug use among needle-exchange users. Drug and Alcohol Dependence. 2001;62(3):225-230.	Ineligible outcome
Bluthenthal RN, Kral AH, Erringer EA, Edlin BR. Use of an illegal syringe exchange and injection-related risk behaviors among street-recruited injection drug users in Oakland, California, 1992 to 1995. Journal of acquired immune deficiency syndromes and human retrovirology : official publication of the International Retrovirology Association. 1998;18(5):505-511.	Ineligible study design
Bluthenthal RN, Kral AH, Gee L, Erringer EA, Edlin BR. The effect of syringe exchange use on high-risk injection drug users: a cohort study. AIDS (London, England). 2000;14(5):605-611.	Ineligible study design
Borquez A, Abramovitz D, Cepeda J, et al. Syringe sharing among people who inject drugs in Tijuana: Before and after the Global Fund. Salud Mental. 2019;42(4):149-156.	Ineligible study design

Citation	Exclude Reason
Bråbäck M, Ekström L, Troberg K, et al. Malmö Treatment Referral and Intervention Study—High 12-Month Retention Rates in Patients Referred from Syringe Exchange to Methadone or Buprenorphine/Naloxone Treatment. Front Psychiatry. 2017;8:161.	Ineligible comparator
Braine N, Des Jarlais DC, Ahmad S, Purchase D, Turner C. Long-Term Effects of Syringe Exchange on Risk Behavior and HIV Prevention. AIDS Education and Prevention. 2004;16(3):264-275.	Ineligible comparator
Bravo MJ, Royuela L, Barrio G, Brugal MT, Domingo A, de la Fuente L. Access to sterile syringes among young drug injectors in Madrid and Barcelona and its association with risk behaviour. Gaceta sanitaria. 2008;22(2):128-132.	Ineligible study design
Bravo MJ, Royuela L, Barrio G, de la Fuente L, Suarez M, Brugal MT. More free syringes, fewer drug injectors in the case of Spain. Social Science & Medicine. 2007;65(8):1773-1778.	Ineligible outcome
Brennan R, Wells JSG, Van Hout MC. The injecting use of image and performance-enhancing drugs (IPED) in the general population: a systematic review. Health & social care in the community. 2017;25(5):1459-1531.	Ineligible outcome
Broz D, Carnes N, Chapin-Bardales J, et al. Syringe services programs' role in ending the HIV epidemic in the U.S.: Why we cannot do it without them. American Journal of Preventive Medicine. 2021;61(5, Suppl 1):S118-S129.	Ineligible publication type
Bruneau J, Brogly SB, Tyndall MW, Lamothe F, Franco EL. Intensity of drug injection as a determinant of sustained injection cessation among chronic drug users: The interface with social factors and service utilization. Addiction. 2004;99(6):727-737.	Ineligible outcome
Bryant J, Topp L, Hopwood M, Iversen J, Treloar C, Maher L. Is point of access to needles and syringes related to needle sharing? Comparing data collected from pharmacies and needle and syringe programs in South-East Sydney. Drug and Alcohol Review. 2010;29(4):364-370.	Ineligible comparator
Buning EC. Effects of Amsterdam needle and syringe exchange. The International journal of the addictions. 1991;26(12):1303-1311.	Ineligible study design
Bushling C, Walton MT, Conner KL, et al. Syringe services programs in the Bluegrass: Evidence of population health benefits using Kentucky Medicaid data. The Journal of rural health : official journal of the American Rural Health Association and the National Rural Health Care Association. 2022;38(3):620-629.	Ineligible outcome
Cardell D. Maintaining the health of sex workers through outreach work. Professional nurse (London, England). 2001;17(1):31.	Ineligible outcome
Carvell AM, Hart GJ. Help-seeking and referrals in a needle exchange: A comprehensive service to injecting drug users. British Journal of Addiction. 1990;85(2):235-240.	Ineligible comparator
Castillo T. Spotlight on the Safety Net: Hepatitis C Virus Infection and Syringe Exchange Programs. North Carolina medical journal. 2016;77(3):224-225.	Ineligible publication type
Clarke K. The case of a needle exchange policy debate in Fresno, California. Critical Social Policy. 2016;36(2):289-306.	Ineligible study design
Clarke K, Harris D, Zweifler JA, Lasher M, Mortimer RB, Hughes S. The Significance of Harm Reduction as a Social and Health Care Intervention for Injecting Drug Users: An Exploratory Study of a Needle Exchange Program in Fresno, California. Social work in public health. 2016;31(5):398-407.	Ineligible study design
Coffin P. Syringe availability as HIV prevention: a review of modalities. Journal of urban health : bulletin of the New York Academy of Medicine. 2000;77(3):306-330.	Outdated or ineligible SR
Cooper H, Des Jarlais D, Ross Z, Tempalski B, Bossak BH, Friedman SR. Spatial access to sterile syringes and the odds of injecting with an unsterile syringe among	Ineligible study design

Citation	Exclude Reason
injectors: a longitudinal multilevel study. Journal of urban health : bulletin of the New York Academy of Medicine. 2012;89(4):678-696.	
Cooper HLF, Des Jarlais DC, Ross Z, Tempalski B, Bossak B, Friedman SR. Spatial access to syringe exchange programs and pharmacies selling over-the-counter syringes as predictors of drug injectors' use of sterile syringes. American journal of public health. 2011;101(6):1118-1125.	Ineligible study design
Crawford ND, Myers S, Young H, Klepser D, Tung E. The Role of Pharmacies in the HIV Prevention and Care Continuums: A Systematic Review. AIDS and behavior. 2021;25(6):1819-1828.	Outdated or ineligible SR
Davis SM. Needle exchange programs to prevent Hepatitis C virus infection in people who inject drugs in rural Appalachia. Dissertation Abstracts International: Section B: The Sciences and Engineering. 2018;79(9-B(E)):No-Specified.	Duplicate
DeCuir J, Lovasi GS, El-Sayed A, Lewis CF. The association between neighborhood socioeconomic disadvantage and high-risk injection behavior among people who inject drugs. Drug and Alcohol Dependence. 2018;183:184-191.	Ineligible study design
Deren S, Naegle M, Hagan H, Ompad DC. Continuing Links Between Substance Use and HIV Highlight the Importance of Nursing Roles. The Journal of the Association of Nurses in AIDS Care : JANAC. 2017;28(4):622-632.	Ineligible publication type
Deryabina AP. An assessment of needle-syringe program for people who inject drugs in the Kyrgyz Republic. Dissertation Abstracts International: Section B: The Sciences and Engineering. 2017;78(2-B(E)):No-Specified.	Ineligible comparator
Des Jarlais DC, Arasteh K, Hagan H, McKnight C, Perlman DC, Friedman SR. Persistence and change in disparities in HIV infection among injection drug users in New York City after large-scale syringe exchange programs. American Journal of Public Health. 2009;99(Suppl 2):S445-S451.	Ineligible study design
Des Jarlais DC, Braine N, Yi H, Turner C. Residual injection risk behavior, HIV infection, and the evaluation of syringe exchange programs. AIDS education and prevention : official publication of the International Society for AIDS Education. 2007;19(2):111-123.	Ineligible comparator
Des Jarlais DC, Feelemyer JP, Modi SN, Abdul-Quader A, Hagan H. High coverage needle/syringe programs for people who inject drugs in low and middle income countries: a systematic review. BMC public health. 2013;13:53.	Outdated or ineligible SR
Des Jarlais DC, Fisher DG, Newman JC, et al. Providing hepatitis B vaccination to injection drug users: referral to health clinics vs on-site vaccination at a syringe exchange program. American journal of public health. 2001;91(11):1791-1792.	Ineligible intervention
Des Jarlais DC, Friedmann P, Grund J-P, et al. HIV risk behaviour among participants of syringe exchange programmes in central/eastern Europe and Russia. International Journal of Drug Policy. 2002;13(3):165-170.	Ineligible comparator
Des Jarlais DC, Kling R, Hammett TM, et al. Reducing HIV infection among new injecting drug users in the China-Vietnam Cross Border Project. AIDS. 2007;21(Suppl8):S109-S114.	Ineligible study design
Des Jarlais DC, Marmor M, Paone D, et al. HIV incidence among injecting drug users in New York City syringe-exchange programmes. Lancet (London, England). 1996;348(9033):987-991.	Ineligible study design
Des Jarlais DC, Perlis T, Arasteh K, et al. Reductions in hepatitis C virus and HIV infections among injecting drug users in New York City, 1990-2001. AIDS (London, England). 2005;19 Suppl 3:S20-25.	Ineligible study design
Des Jarlais DC, Sloboda Z, Friedman SR, Tempalski B, McKnight C, Braine N. Diffusion of the D.A.R.E and Syringe Exchange Programs. American Journal of Public Health. 2006;96(8):1354-1357.	Ineligible publication type

Citation	Exclude Reason
Dickson NP, Austin FJ, Paul C, Sharples KJ, Skegg DC. HIV surveillance by testing saliva from injecting drug users: a national study in New Zealand. Journal of epidemiology and community health. 1994;48(1):55-57.	Ineligible comparator
Dolan KA, Donoghoe MC, Stimson GV. Reductions in HIV risk behaviour and stable HIV prevalence in syringe-exchange clients and other injectors in England. Drug and alcohol review. 1993;12(2):133-142.	Ineligible outcome
Dolan K, Rutter S, Wodak AD. Prison-based syringe exchange programmes: A review of international research and development. Addiction. 2003;98(2):153-158.	Outdated or ineligible SR
Drucker E, Lurie P, Wodak A, Alcabes P. Measuring harm reduction: the effects of needle and syringe exchange programs and methadone maintenance on the ecology of HIV. AIDS (London, England). 1998;12 Suppl A:S217-230.	Outdated or ineligible SR
Durante AJ, Hart GJ, Brady AR, Madden PB, Noone A. The Health of the Nation target on syringe sharing: A role for routine surveillance in assessing progress and targeting interventions. Addiction. 1995;90(10):1389-1396.	Ineligible study design
Dutta A, Wirtz AL, Baral S, Beyrer C, Cleghorn FR. Key harm reduction interventions and their impact on the reduction of risky behavior and HIV incidence among people who inject drugs in low-income and middle-income countries. Current opinion in HIV and AIDS. 2012;7(4):362-368.	Ineligible study design
Fernando D. Syringe and needle exchange to prevent HIV infection. JAMA. 1994;271(23):1825-1827.	Ineligible publication type
Fisher DG, Fenaughty AM, Cagle HH, Reynolds GL. Injection drug users' use of pharmacies for purchasing needles in Anchorage, Alaska. Special Issue: Sterile Syringe Access for Injection Drug Users in the 21st Century: Progress and prospects. 2003;14(5-6):381-387.	Ineligible comparator
Fisher DG, Harbke CR, Canty JR, Reynolds GL. Needle and syringe cleaning practices among injection drug users. Journal of Drug Education. 2002;32(2):167-178.	Ineligible study design
Fisher DG, Reynolds GL, Harbke CR. Selection effect of needle exchange in Anchorage, Alaska. Journal of urban health : bulletin of the New York Academy of Medicine. 2002;79(1):128-135.	Ineligible outcome
Frangakis CE, Brookmeyer RS, Varadhan R, Safaeian M, Vlahov D, Strathdee SA. Methodology for Evaluating a Partially Controlled Longitudinal Treatment Using Principal Stratification, With Application to a Needle Exchange Program. Journal of the American Statistical Association. 2004;99(465):239-249.	Ineligible publication type
Franken IH, Kaplan CD. Risk contexts and risk behaviors in the Euregion Maas-Rhein: the Boule de Neige intervention for AIDS prevention among drug users. AIDS education and prevention : official publication of the International Society for AIDS Education. 1997;9(2):161-180.	Unable to locate FT
Friedman SR, West BS, Tempalski B, et al. Do metropolitan HIV epidemic histories and programs for people who inject drugs and men who have sex with men predict AIDS incidence and mortality among heterosexuals? Annals of epidemiology. 2014;24(4):304-311.	Ineligible study design
Frischer M, Elliott L, Taylor A, et al. Do needle exchanges help to control the spread of HIV among injecting drug users? AIDS (London, England). 1993;7(12):1677-1678.	Ineligible study design
Frischer M, Taylor A, Goldberg D, Elliott L. Direct evaluation of needle and syringe exchange programmes. Lancet (London, England). 1996;347(9003):768.	Ineligible study design
Gagnon H, Godin G, Alary M, Bruneau J, Otis J. A randomized trial to evaluate the efficacy of a computer-tailored intervention to promote safer injection practices among drug users. AIDS & Behavior. 2010;14(3):538-548.	Ineligible intervention

Citation	Exclude Reason
Gibson DR, Flynn NM, Perales D. Effectiveness of syringe exchange programs in reducing HIV risk behavior and HIV seroconversion among injecting drug users. AIDS (London, England). 2001;15(11):1329-1341.	Outdated or ineligible SR
Gibson EK, Exner H, Stone R, Lindquist J, Cowen L, Roth EA. A mixed methods approach to delineating and understanding injection practices among clientele of a Victoria, British Columbia needle exchange program. Drug and Alcohol Review. 2011;30(4):360-365.	Ineligible study design
Gicquelais RE, Genberg BL, Astemborski J, Celentano DD, Kirk GD, Mehta SH. Association of Injection Practices and Overdose With Drug Use Typologies: A Latent Class Analysis Among People Who Inject Drugs in Baltimore, 2017. AIDS Education & Prevention. 2019;31(4):344-362.	Ineligible outcome
Goldberg D, Burns S, Taylor A, Cameron S, Hargreaves D, Hutchinson S. Trends in HCV prevalence among injecting drug users in Glasgow and Edinburgh during the era of needle/syringe exchange. Scandinavian journal of infectious diseases. 2001;33(6):457-461.	Ineligible study design
Golub ET, Strathdee SA, Bailey SL, et al. Distributive syringe sharing among young adult injection drug users in five U.S. Cities. Drug and Alcohol Dependence. 2007;91(Suppl 1):S30-S38.	Ineligible study design
Gostin LO, Lazzarini Z. Prevention of HIV/AIDS among injection drug users: the theory and science of public health and criminal justice approaches to disease prevention. Emory law journal. 1997;46(2):587-696.	Ineligible publication type
Gray J. Operating needle exchange programmes in the hills of Thailand. AIDS Care. 1995;7(4):489-499.	Ineligible study design
Gray J. Harm reduction in the hills of Northern Thailand. Special Issue: Needle exchange policy and practice: International perspective. 1998;33(5):1075-1091.	Ineligible study design
Gruer L, Cameron J, Elliott L. Building a city wide service for exchanging needles and syringes. BMJ (Clinical research ed). 1993;306(6889):1394-1397.	Ineligible comparator
Guenter CD, Fonseca K, Nielsen DM, Wheeler VJ, Pim CP. HIV prevalence remains low among Calgary's needle exchange program participants. Canadian journal of public health = Revue canadienne de sante publique. 2000;91(2):129-132.	Ineligible comparator
Guydish J, Bucardo J, Clark G, Bernheim S. Evaluating needle exchange: a description of client characteristics, health status, program utilization, and HIV risk behavior. Substance use & misuse. 1998;33(5):1173-1196.	Ineligible study design
Guydish J, Bucardo J, Young M, Woods W, Grinstead O, Clark W. Evaluating needle exchange: are there negative effects? AIDS (London, England). 1993;7(6):871-876.	Ineligible comparator
Hagan H, Des Jarlais DC, Purchase D, Reid T, Friedman SR. The Tacoma Syringe Exchange. Journal of Addictive Diseases. 1991;10(4):81-88.	Ineligible publication type
Hagan H, Jarlais DC, Friedman SR, Purchase D, Alter MJ. Reduced risk of hepatitis B and hepatitis C among injection drug users in the Tacoma syringe exchange program. American journal of public health. 1995;85(11):1531-1537.	Ineligible study design
Hagan H, McGough JP, Thiede H, Weiss NS, Hopkins S, Alexander ER. Syringe exchange and risk of infection with hepatitis B and C viruses. American journal of epidemiology. 1999;149(3):203-213.	Ineligible study design
Hagan H, Reid T, Des Jarlais DC, Purchase D, Friedman SR, Bell TA. The incidence of HBV infection and syringe exchange programs. JAMA. 1991;266(12):1646-1647.	Ineligible publication type
Hagan H, Thiede H. Changes in injection risk behavior associated with participation in the Seattle needle-exchange program. Journal of urban health : bulletin of the New York Academy of Medicine. 2000;77(3):369-382.	Ineligible study design

Citation	Exclude Reason
Hainsworth SW, Dietze PM, Wilson DP, Sutton B, Hellard ME, Scott N. Hepatitis C virus notification rates in Australia are highest in socioeconomically disadvantaged areas. PloS one. 2018;13(6):e0198336.	Ineligible study design
Handanagic S, Sevic S, Barbaric J, et al. Correlates of anti-hepatitis C positivity and use of harm reduction services among people who inject drugs in two cities in Croatia. Drug and alcohol dependence. 2017;171:132-139.	Ineligible study design
Hart GJ, Carvell AL, Woodward N, Johnson AM, Williams P, Parry JV. Evaluation of needle exchange in central London: Behaviour change and anti-HIV status over one year. AIDS. 1989;3(5):261-265.	Ineligible study design
Heimer R. Can syringe exchange serve as a conduit to substance abuse treatment? Journal of Substance Abuse Treatment. 1998;15(3):183-191.	Ineligible comparator
Heimer R. Community coverage and HIV prevention: Assessing metrics for estimating HIV incidence through syringe exchange. International Journal of Drug Policy. 2008;19(S).	Ineligible outcome
Heimer R, Kaplan EH, Khoshnood K, Jariwala B, Cadman EC. Needle exchange decreases the prevalence of HIV-1 proviral DNA in returned syringes in New Haven, Connecticut. The American journal of medicine. 1993;95(2):214-220.	Ineligible study design
Heimer R, Khoshnood K, Bigg D, Guydish J, Junge B. Syringe use and reuse: effects of syringe exchange programs in four cities. Journal of acquired immune deficiency syndromes and human retrovirology : official publication of the International Retrovirology Association. 1998;18 Suppl 1:S37-44.	Ineligible comparator
Henderson LA, Vlahov D, Celentano DD, Strathdee SA. Readiness for cessation of drug use among recent attenders and nonattenders of a needle exchange program. Journal of acquired immune deficiency syndromes (1999). 2003;32(2):229-237.	Ineligible outcome
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Strathdee SA, Ricketts EP, Huettner S, et al. Facilitating entry into drug treatment among injection drug users referred from a needle exchange program: Results from a community-based behavioral intervention trial. Drug and Alcohol Dependence. 2006;83(3):225-232.	Ineligible intervention
Strenski TA, Marshall PA, Gacki JK, Sanchez CW. The emergent impact of syringe exchange programs on shooting galleries and injection behaviors in three ethnically diverse Chicago neighborhoods. Special Issue: Emergent trends in illicit drug-use behaviors. 2000;18(4):415-438.	Unable to locate FT

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Strike C, Miskovic M. Scoping out the literature on mobile needle and syringe programs-review of service delivery and client characteristics, operation, utilization, referrals, and impact. Harm reduction journal. 2018;15(1):6.	Ineligible publication type
Strike C, Rudzinski K, Patterson J, Millson M. Frequent food insecurity among injection drug users: correlates and concerns. BMC public health. 2012;12:1058.	Ineligible intervention
Telles PR. Preventing HIV/AIDS and other sexually transmitted diseases among injecting drug users in Rio de Janeiro. International Journal of Drug Policy. 1999;10(5):365-373.	Ineligible outcome
Tempalski B, Beane S, Cooper HLF, et al. Structural determinants of Black MSM HIV testing coverage (2011-2016). AIDS and Behavior. 2020;24(9):2572-2587.	Ineligible outcome
Todd CS, Nasir A, Stanekzai MR, et al. Hepatitis C and HIV incidence and harm reduction program use in a conflict setting: an observational cohort of injecting drug users in Kabul, Afghanistan. Harm reduction journal. 2015;12:22.	Ineligible study design
Todd CS, Stibich MA, Stanekzai MR, et al. A qualitative assessment of injection drug use and harm reduction programmes in Kabul, Afghanistan: 2006-2007. International Journal of Drug Policy. 2009;20(2):111-120.	Ineligible outcome
Tomolillo CM, Crothers LJ, Aberson CL. The damage done: A study of injection drug use, injection related abscesses and needle exchange regulation. Substance Use & Misuse. 2007;42(10):1603-1611.	Ineligible outcome
Tookes H, Bartholomew TS, Geary S, et al. Rapid identification and investigation of an HIV risk network among people who inject drugs -Miami, FL, 2018. AIDS and Behavior. 2020;24(1):246-256.	Ineligible intervention
Tookes HE, Oxner A, Serota DP, et al. Project T-SHARP: study protocol for a multi-site randomized controlled trial of tele-harm reduction for people with HIV who inject drugs. Trials. 2023;24(1):96.	Ineligible intervention
Tortu S, Deren S, Beardsely M, Hamid R. Factors associated with needle exchange use in East Harlem, New York City. Journal of Drug Issues. 1996;26(4):735-749.	Unable to locate FT
Tsai R, Goh EH, Webeck P, Mullins J. Prevention of human immunodeficiency virus infection among intravenous drug users in New South Wales, Australia: the needles and syringes distribution programme through retail pharmacies. Asia-Pacific journal of public health. 1988;2(4):245-251.	Ineligible outcome
Uuskula A, Des Jarlais DC, Raag M, Pinkerton SD, Feelemyer J. Combined prevention for persons who inject drugs in the HIV epidemic in a transitional country: The case of Tallinn, Estonia. AIDS Care. 2015;27(1):105-111.	Ineligible publication type
Uuskula A, McMahon JM, Raag M, et al. Emergent properties of HIV risk among injection drug users in Tallinn, Estonia: synthesis of individual and neighbourhood-level factors. Sexually transmitted infections. 2010;86 Suppl 3:iii79-84.	Ineligible study design
Valenciano M, Emmanuelli J, Lert F. Unsafe injecting practices among attendees of syringe exchange programmes in France. Addiction. 2001;96(4):597-606.	Ineligible comparator
van Ameijden EJ, van den Hoek AR, Coutinho RA. Injecting risk behavior among drug users in Amsterdam, 1986 to 1992, and its relationship to AIDS prevention programs. American journal of public health. 1994;84(2):275-281.	Ineligible study design
van den Berg C, Smit C, van Brussel G, Coutinho R, Prins M. Full participation in harm reduction programmes is associated with decreased risk for human immunodeficiency virus and hepatitis C virus: Evidence from the Amsterdam Cohort Studies among drug users. Addiction. 2007;102(9):1454-1462.	Ineligible study design
van den Hoek JA, van Haastrecht HJ, Coutinho RA. Risk reduction among intravenous drug users in Amsterdam under the influence of AIDS. American journal of public health. 1989;79(1):1355-1357.	Ineligible intervention

Citation	Exclude Reason
van der Meulen E, Watson TM, De Shalit A. Insights on prison needle and syringe programs: Research with former prisoners in Canada. The Prison Journal. 2017;97(5):628-643.	Ineligible comparator
van Santen DK, Boyd A, Matser A, et al. The effect of needle and syringe program and opioid agonist therapy on the risk of HIV, hepatitis B and C virus infection for people who inject drugs in Amsterdam, the Netherlands: findings from an emulated target trial. Addiction. 2021;116(11):3115-3126.	Ineligible study design
van Santen DK, Coutinho RA, van den Hoek A, van Brussel G, Buster M, Prins M. Lessons learned from the Amsterdam Cohort Studies among people who use drugs: A historical perspective. Harm Reduction Journal. 2021;18.	Ineligible study design
van Santen DK, Lodi S, Dietze P, et al. Comprehensive needle and syringe program and opioid agonist therapy reduce HIV and hepatitis c virus acquisition among people who inject drugs in different settings: A pooled analysis of emulated trials. Addiction (Abingdon, England). 2023.	Ineligible study design
Vlahov D, Brookmeyer RS. The evaluation of needle exchange programs. American journal of public health. 1994;84(12):1889-1891.	Ineligible publication type
Vlahov D, Junge B. The role of needle exchange programs in HIV prevention. Public health reports (Washington, DC : 1974). 1998;113 Suppl 1:75-80.	Ineligible publication type
Vlahov D, Robertson AM, Strathdee SA. Prevention of HIV infection among injection drug users in resource-limited settings. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2010;50 Suppl 3:S114-121.	Ineligible publication type
Vlahov D, Ryan C, Solomon L, Cohn S, Holt MR, Akhter MN. A pilot syringe exchange program in Washington, DC. American Journal of Public Health. 1994;84(2):303-304.	Ineligible comparator
Watson DP, Swartz JA, Robison-Taylor L, et al. Syringe service program-based telemedicine linkage to opioid use disorder treatment: protocol for the STAMINA randomized control trial. BMC public health. 2021;21(1):630.	Ineligible publication type
Werb D, Kerr T, Buxton J, et al. Patterns of injection drug use cessation during an expansion of syringe exchange services in a Canadian setting. Drug and alcohol dependence. 2013;132(3):535-540.	Ineligible outcome
White RH, O'Rourke A, Kilkenny ME, et al. Prevalence and correlates of receptive syringe-sharing among people who inject drugs in rural Appalachia. Addiction. 2021;116(2):328-336.	Ineligible study design
Whiteman A, Burnett J, Handanagic S, Wejnert C, Broz D. Distance matters: The association of proximity to syringe services programs with sharing of syringes and injecting equipment-17 U.S. cities, 2015. International Journal of Drug Policy. 2020;85.	Ineligible study design
Wiessing L, Likatavicius G, Klempová D, Hedrich D, Nardone A, Griffiths P. Associations between availability and coverage of HIV-prevention measures and subsequent incidence of diagnosed HIV infection among injection drug users. American Journal of Public Health. 2009;99(6):1049-1052.	Ineligible study design
Wodak A. Lessons From the First International Review of the Evidence for Needle Syringe Programs: The Band Still Plays On. Special Issue: Syringe Access and Secondary Syringe Exchange: International Perspectives and Future Directions. 2006;41(6-7):837-839.	Ineligible publication type
Wodak A, Cooney A. Do Needle Syringe Programs Reduce HIV Infection Among Injecting Drug Users: A Comprehensive Review of the International Evidence. Special Issue: Syringe Access and Secondary Syringe Exchange: International Perspectives and Future Directions. 2006;41(6-7):777-813.	Outdated or ineligible SR

Citation	Exclude Reason
Wolk J, Wodak A, Guinan JJ, Macaskill P, Simpson JM. The effect of a needle and syringe exchange on a methadone maintenance unit. British Journal of Addiction. 1990;85(1):1445-1450.	Ineligible outcome
Wood E, Lloyd-Smith E, Li K, et al. Frequent needle exchange use and HIV incidence in Vancouver, Canada. The American journal of medicine. 2007;120(2):172-179.	Ineligible study design
Wood E, Tyndall MW, Spittal PM, et al. Factors associated with persistent high-risk syringe sharing in the presence of an established needle exchange programme. AIDS. 2002;16(6):941-943.	Unable to locate FT
Wu Q, Kamphuis C, Duo L, Luo J, Chen Y, Richardus JH. Coverage of harm reduction services and HIV infection: A multilevel analysis of five Chinese cities. Harm Reduction Journal. 2017;14.	Ineligible study design
Yang C-H, Yang S-Y, Shen M-H, Kuo H-S. The changing epidemiology of prevalent diagnosed HIV infections in Taiwan, 1984-2005. International Journal of Drug Policy. 2008;19(4):317-323.	Ineligible study design
Yee WL, Draper B, Myint KT, et al. Access to needles and syringes and methadone maintenance therapy among people who inject drugs in Yangon, Myanmar: a qualitative study. Harm reduction journal. 2022;19(1):107.	Ineligible comparator
Yoast R, Williams MA, Deitchman SD, Champion HC. Report of the Council on Scientific Affairs: Methadone maintenance and needle-exchange programs to reduce the medical and public health consequences of drug abuse. Journal of Addictive Diseases. 2001;20(2):15-40.	Ineligible publication type
Zaw C, Mehra D. The efficacy of syringe services programs in reducing skin and soft tissue infection-associated healthcare costs and multidrug-resistant bacteria. American journal of infection control. 2020;48(4):467-468.	Ineligible publication type

UNDERWAY STUDIES

Citation
NCT02654366. Community Supported Risk Reduction for Syringe Exchange Participants. CN-01555077. https://clinicaltrials.gov/show/NCT02654366.
NCT01557998. Testing and Linkage to Care for Injecting Drug Users in Kenya. CN-01591363. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01591363/full.

CHARACTERISTICS OF INCLUDED PRIMARY STUDIES

Study	City/State Country	Sample Size *Follow-up*	Participant Characteristics	Non-Prescribed Substance(s) Use	Intervention/Exposure and Comparator (if applicable)	Included Outcome(s)
RCTs						
Braback 2016[85]	Skane Sweden	N=75 *NR*	Mean age: 37 % Male: 73 Race/ethnicity NR	Heroin	SSP clients receiving a strength-based case management intervention to facilitate treatment referral compared to SSP clients receiving referral only	Linkage to treatment/utilization of referred services[a]
Fisher 2003[3]	Alaska US	N=600 *12 mos*	Mean age: 39 % Male: 76 % AA/Black: 19 % Native American: 20 % Other: 5 % White: 56	Heroin, cocaine, speedball, other opioids, amphetamines	Randomized to SSP access or training on acquiring needles from pharmacies	Injection frequency
Lewis 2015[b] [29]	New York, NY US	N=592 *3 mos*	Mean age: 44 % Male: 69 % AA/Black: 29 % Hispanic: 51 % White: 16	NR	Pharmacies that received harm reduction training and provided additional services compared to pharmacies providing usual care	Unsafe disposal of syringes
Cohort Studies						
Brooner 1998[28,87]	Baltimore, MD US	N=325 *1 yr*	Mean age: 38 % Male: 50 % White: 41	Heroin, cocaine, sedative, cannabis	Referred to OAT from SSP compared to other referral sources	Linkage to treatment/utilization of referred services
Hagan 2000[4]	Seattle, WA US	N=Variable *1 yr*	Age NR % Male: 62 % AA/Black: 20 % Other: 11 % White: 69	Heroin, speedball, cocaine, amphetamines	Current exchange users, new exchange users, ex-exchangers compared to never exchangers	Injection frequency, linkage to treatment/utilization of referred services
Hartgers 1989[5]	Amsterdam, Netherlands	N=54 *Mean 13.5 mos*	Mean age: 32 % Male: 70 NR	Heroin, cocaine, methadone, hashish, marijuana, tranquillizers, amphetamines	Regular exchangers (used SSP > 90% of the time) compared to irregular exchangers or non-exchangers	Injection frequency, linkage to treatment/utilization of referred services
Huo 2006[9]	Chicago, IL US	N=707 *3 yrs*	Mean age: 40 % Male: 71 % AA/Black: 44 % Non-AA/Black: 55	Heroin, speedball, powder/crack cocaine	SSP users (used SSP at least twice ever and enrolled for at least 30 days) compared to non-SSP users	Injection frequency

Study	City/State Country	Sample Size *Follow-up*	Participant Characteristics	Non-Prescribed Substance(s) Use	Intervention/Exposure and Comparator (if applicable)	Included Outcome(s)
Kuo 2003[26]	Baltimore, MD US	N=163 *3 mos*	Mean age: 43 % Male: 68 % AA/Black: 99	Heroin, cocaine	Duration and frequency of SSP use	Linkage to treatment/utilization of referred services
Latkin 2006[25]	Baltimore, MD US	N=440 *Average 15 mos*	57% age >39 yrs % Male: 68 % AA/Black: 94	Heroin, speedball, powder/crack cocaine	Current SSP utilization (past 6 mo) compared to no SSP use	Linkage to treatment/utilization of referred services
Marmor 2000[6]	New York, NY US	N=328 *Median 29.7 mos*	Mean age: 40 % Male: 78 29% AA/Black: 29 % Asian: <1 % Hispanic: 28 % Native American: <1 % Other: <1 % White: 42	Heroin, powder/crack cocaine, marijuana	Consistent or sporadic SSP users compared to no SSP use	Injection frequency
Monterroso 2000[7]	Multiple US	N=2,306 *Mean 7.8 mos*	Mean age: 38 % Male: 63 % AA/Black: 43 % Hispanic: 32 % White: 21	NR	Ever used an SSP compared to never used an SSP	Injection frequency
Schoenbaum 1996[8]	New York, NY US	N=329 *5 yrs*	Median age: 30 % Male: 65 % Black: 17 % Hispanic: 67 % White: 16	Heroin, cocaine, speedball	Ever used an SSP compared to never used an SSP	Injection frequency
Strathdee 1999[27,86]	Baltimore, MD US	N=1,483 *4.5 yrs*	Median age: 40 % Male: 74 % AA/Black: 95 % Non-AA/Black: 5	Heroin, cocaine, speedball	SSP attendance compared to no attendance	Linkage to treatment/utilization of referred services
Pre-Post Studies						
Bartholomew 2021[10]	Miami, FL US	N=115 *Variable*	Median age: 38 % Male: 77 % Hispanic: 45 % Non-Hispanic Black: 4 % Non-Hispanic White: 50	Heroin, powder/crack cocaine, methamphetamine, speedball, fentanyl	SSP clients	Injection frequency

Study	City/State Country	Sample Size *Follow-up*	Participant Characteristics	Non-Prescribed Substance(s) Use	Intervention/Exposure and Comparator (if applicable)	Included Outcome(s)
Cox 2000[11]	Ireland	N=370 *3 mos*	Mean age: 23 % Male: 79 Race/ethnicity NR	Heroin	SSP attendance	Injection frequency, linkage to treatment/utilization of referred services
Donoghoe 1989[12]	England and Scotland	N=142 *Variable*	Mean age: 30 % Male: 86 Race/ethnicity: NR	Heroin, methadone, amphetamine, cocaine, barbiturates, tranquillizers, others	Attendance at an SSP at least once during the 1 year period prior to the study	Injection frequency
Iversen 2013[13]	Multiple Australia	N=724 *Variable*	Mean age: 32 % Male: 65 Race/ethnicity NR	Methamphetamine, heroin, cocaine, methadone or buprenorphine, pharmaceutical opioids, others	SSP users across 3 time periods	Injection frequency
Patel 2018[14]	Indiana US	N=148 *Median 10 wks*	Median age: 34 % Male: 56 % Non-Hispanic White: 98 % Other: 2	Opana, heroin, methamphetamines, others	SSP clients at first and most recent visit to the SSP	Injection frequency
Schechter 1999[15]	Vancouver Canada	N=694 *6 mos*	Median age: 36 % Male: 68 % Aboriginal: 25 % Other: 10 % White: 65	Heroin, cocaine	Frequent SSP attendance compared to no attendance	Injection frequency
Vertefeuille 2000[16]	Baltimore, MD US	N=112 *6 mos*	Mean age: 40 % Male: 71 % AA/Black: 89 % Other: 11	Heroin, cocaine, speedball	SSP enrollees	Injection frequency, linkage to treatment/utilization of referred services, unsafe disposal of syringes
Vlahov 1997[17]	Baltimore, MD US	N=422 *6 mos*	Mean age: 38 % Male: 67 % AA/Black: 87	Heroin, speedball, cocaine	SSP enrollees	Injection frequency, linkage to treatment/utilization of referred services, unsafe disposal of syringes
Vogt 1998[18]	Hawaii US	N=208 *NR*	NR	NR	SSP attenders	Injection frequency

Study	City/State Country	Sample Size *Follow-up*	Participant Characteristics	Non-Prescribed Substance(s) Use	Intervention/Exposure and Comparator (if applicable)	Included Outcome(s)
Cross-Sectional Studies						
Allen 2021[20]	Cabell County, WV US	N=420 *NA*	Mean age: 36 % Male: 61 % Non-Hispanic White: 84	Heroin, fentanyl, buprenorphine or Suboxone, prescription opioid, crystal methamphetamine, speedball, cocaine	Acquired sterile syringes from an SSP in the past 6 mos compared to those who did not	Naloxone distribution or use
Bluthenthal 2004[32,107]	Multiple US	N=584 *NA*	Mean age: 41 % Male: 58 % AA/Black: 41 % Hispanic: 38 % Other: 2 % White: 18	Heroin, speedball, amphetamine, powder/crack cocaine	Residence in cities with more permissive exchange policies compared to residence in city with less permissive exchange policy	Unsafe disposal of syringes
Cleland 2007[30]	New York US	N=1,030 *NA*	Mean age: 37 % Male: 72 % AA/Black: 13 % Hispanic: 77 % White: 11	Heroin, powder/crack cocaine	Obtained syringe used for last injection from SSP or source related to ESAP (*ie*, pharmacy, hospital, clinic, doctor) compared to other source	Unsafe disposal of syringes
Coffin 2007[33]	Multiple US	N=680 *NA*	Mean age: 42 % Male: 62 % AA/Black: 59 % Hispanic: 21 % Other: 9 % White: 12	Heroin, powder/crack cocaine	Ever used an SSP or safe syringe source compared to never used an SSP or unsafe syringe source	Unsafe disposal of syringes
Cotton-Oldenburg 2001[31]	Minnesota US	N=570 *NA*	Mean age: 37 % Male: 66 % AA/Black: 36 % American Indian: 9 % Asian: 1 % Hispanic: 14 % Other: 3 % White: 37	Heroin, cocaine, speedball, methamphetamine, others	Time period (9-12 mos) before and after legislation allowing for legal sale of syringes by pharmacies without a prescription	Unsafe disposal of syringes
Dasgupta 2019[34]	Indiana US	N=200 *NA*	18-25: 13% 25-34: 35% 35-44: 31% ≥45: 31% % Male: 58 % Hispanic: 2	Opana, methamphetamine, heroin, other prescription opioid	Time period before and after start of large-scale public health response to HIV outbreak including establishment of SSP	Unsafe disposal of syringes

Study	City/State Country	Sample Size *Follow-up*	Participant Characteristics	Non-Prescribed Substance(s) Use	Intervention/Exposure and Comparator (if applicable)	Included Outcome(s)
			% Multiracial: 5 % White: 92			
Jones 2021[21]	Baltimore, MD US	N=263 *NA*	18-44: 42% ≥45: 58% % Male: 70 % AA/Black: 61 % White: 39	Heroin, speedball, marijuana tranquilizer	Registered SSP client compared to non-client peers	Naloxone distribution or use, knowledge of overdose risk
Khoshnood 2000[35]	New Haven, CT US	N=373 *NA*	Mean age: 40 % Male: 64 % AA/Black: 37 % Hispanic: 16 % White: 44	Heroin	Usual syringe source SSP, pharmacy, or both during past 6 mos compared to other source	Unsafe disposal of syringes
Kim 2021[24]	San Francisco, CA US	N=458 *NA*	Mean age: 46 % Male: 68 % AA/Black: 26 % Asian/Pacific Islander: 7 % Hispanic: 15 % Native American/Alaska Native: 16 % White: 67	Opioid, methamphetamine	Received needles or syringes from an SSP in the past 12 mos compared to not receiving needles or syringes from SSP	Knowledge of overdose risk
Quinn 2014[36]	Los Angeles, CA US	N=412 *NA*	Median age: 50 % Male: 69 % AA/Black: 30 % Hispanic: 41 % Other: 9 % White: 21	Heroin, powder/crack cocaine, methamphetamine, tranquilizers, opiates, methadone	Primary source of syringes past 12 mos SSP or pharmacy compared to other source	Unsafe disposal of syringes
Reed 2019[22]	Philadelphia, PA US	N=571 *NA*	Median age: 35 % Male: 78 % AA/Black: 12 % Hispanic: 21 % Other: 3 % White: 64	Heroin, speedball, powder/crack cocaine, methamphetamine, opioid analgesics, benzodiazepines	Primary source of syringes past 6 mos SSP compared to pharmacy or other source in the past 12 mos	Naloxone distribution or use
Riley 2010[37]	San Francisco, CA US	N=105 *NA*	Median age: 42 % Male: 67 % AA/Black: 14 % Hispanic: 12	Heroin, methamphetamine/speed	Obtained syringes from an SSP or pharmacy in the past 30 days compared to not obtaining syringes from an SSP or pharmacy in the past 30 days	Unsafe disposal of syringes

Study	City/State Country	Sample Size *Follow-up*	Participant Characteristics	Non-Prescribed Substance(s) Use	Intervention/Exposure and Comparator (if applicable)	Included Outcome(s)
			% Other: 18 % White: 51			
Sherman 2004[38]	Baltimore, MD US	N=294 *NA*	Median age: 25 % Male: 58 % AA/Black: 30 % Other: 3 % White: 67	Heroin, powder/crack cocaine	Safe acquisition of syringes (primarily obtaining syringes from an SSP or pharmacy) compared with unsafe acquisition of syringes (primarily obtaining syringes from other sources) past 6 mos	Unsafe disposal of syringes
Spring 2022[23]	Multiple UK	N=2,139 *NA*	Mean age: 40 % Male: 72 Race/ethnicity: NR	Heroin, benzodiazepines, others	Past-year contact with SSP compared to no past-year contact with SSP	Naloxone distribution or use
Turner-Bicknell 2021[19]	Ohio US	N=NR *NA*	NR	NR	Before and after implementation of a needs-based distribution model	Naloxone distribution or use
Wood 2003[39]	Vancouver Canada	N=587 *NA*	Median age: 39 for SSP users; 40 for non-SSP users % Male: 61 % Aboriginal: 32 % non-Aboriginal: 68	Heroin, cocaine	Use of all-night SSP in past 6 mos (includes people who used the city's fixed exchange sites) compared to non-use of SSP	Unsafe disposal of syringes
Zlotorzynska 2018[40]	Multiple US	N=6,321 *NA*	Mean age: 43 % Male: 72 % non-Hispanic White: 45 % Other: 55	Heroin, speedball, powder/crack cocaine, methamphetamines, prescription opioids, others	Primary syringe source SSP compared to pharmacy past 12 mos	Unsafe disposal of syringes
Ecological Studies						
Broadhead 1999[44]	Connecticut US	N=NA *NA*	NA	NR	Time period during operation of an SSP compared to time period following closure of the SSP	Unsafe disposal of syringes
Cooper 2012[48]	New York, NY US	N=42 health districts *NA*	NA	NR	SSP access (percent of each district's surface area within 1 mile of an SSP site) or access to pharmacies selling syringes by study year	Neighborhood crime rates
Doherty 1997[45,88]	Baltimore, MD US	N=32 city blocks *2 yrs*	NA	NR	1 and 2 mos after SSP initiation compared to time prior to SSP initiation	Unsafe disposal of syringes
Fuller 2002[46]	New York, NY US	N=27 blocks and 10 pharmacies *NA*	NA	NR	Time period before and after enactment of ESAP (legal pharmacy sale of syringes without a prescription)	Unsafe disposal of syringes

Study	City/State Country	Sample Size *Follow-up*	Participant Characteristics	Non-Prescribed Substance(s) Use	Intervention/Exposure and Comparator (if applicable)	Included Outcome(s)
Marx 2000[49]	Baltimore, MD US	N=NA *NA*	NA	NR	Program areas (within 0.5-mile radius of SSP site) before and after establishment of SSPs and compared to non-program areas	Neighborhood crime rates
Oliver 1992[47]	Portland, OR US	N=NA *NA*	NA	NR	Immediate vicinity of an SSP before and after establishment	Unsafe disposal of syringes
Ecological and Cross-Sectional Studies						
Levine 2019[41]	Miami, Fl US	N=930 *NA*	18-29: 12.7% 30-39: 26.3% 40-49: 27.9% ≥50: 33.3% % Male: 78 % Asian or Pacific Islander: 1 % Hispanic: 40 % Multiple races/Other: 1 % Native American: 2 % non-Hispanic Black: 32 % non-Hispanic White: 26	NR	City residence pre- and post-implementation of the SSP	Unsafe disposal of syringes
Tookes 2012[42]	Multiple US	N=1,050 *NA*	San Francisco: 18-29: 6% 30-39: 18% 40-49: 41% ≥50: 35% % Male: 73 % Asian or Pacific Islander: < 1 % Hispanic: 10 % Multiple races/Other: 5 % Native American: 4 % non-Hispanic Black: 37 % non-Hispanic White: 44 Miami: 18-29: 8% 30-39: 20% 40-49: 31% ≥50: 45% % Male: 79 % Asian or Pacific Islander: 1	NR	City with an SSP and residents of city with an SSP compared to city without an SSP and residents of city without an SSP	Unsafe disposal of syringes

Study	City/State Country	Sample Size *Follow-up*	Participant Characteristics	Non-Prescribed Substance(s) Use	Intervention/Exposure and Comparator (if applicable)	Included Outcome(s)
			% Hispanic: 40 % Native American: 1 % non-Hispanic Black: 36 % non-Hispanic White: 23			
Wenger 2011[43]	San Francisco, CA US	N=602 *NA*	NR	NR	Syringe source SSP or pharmacy prior 6 mos compared to other source	Unsafe disposal of syringes

Notes. [a] This study was included for a comparison relevant to KQ1a; [b] Data for the outcome of interest were cross-sectional.

Abbreviations. AA=African-American; AIDS=acquired immunodeficiency syndrome; ESAP=Expanded Syringe Access Demonstration Program; HIV=human immunodeficiency virus; MMT=methadone maintenance treatment; mos=months; NA=not applicable; NR=not reported; OAT=opioid agonist therapy; RCT=randomized controlled trial; SSP=syringe services program; wks=weeks.

RISK OF BIAS ASSESSMENTS

RANDOMIZED CONTROLLED TRIALS (ROB-2)

Trial Name or Author Year	Bias from randomization process	Bias from deviation from intended interventions (Assignment)	Bias from deviation from intended interventions (Adherence)	Bias from missing outcome data	Bias in measurement of outcome	Bias in selection of reported result	Overall risk of bias (Low, Some concerns, High)
Braback 2016[85]	Low Computer generated block randomization with allocation concealed	Some concerns Participants were likely unblinded, unclear if carers were blinded. Unclear if there were deviations in intervention.	Some concerns Participants were likely unblinded, unclear if carers were blinded. Intervention occurred right after initial assessment, so likely adhered to.	Low Low number of dropouts and regarded as non-attenders	Low Outcome measured as showing up for treatment in both groups.	Low Main outcome reported	Some concerns
Fisher 2003[3]	Low Concealed randomization by a separate person	Some concerns Patients and intervention administrators unblinded at time of giving intervention. Unclear if there were deviations in intervention.	Some concerns Participants were likely unblinded, unclear if carers were blinded. Intervention occurred right after initial assessment, so likely adhered to.	Some concerns Unclear what the "305 complete observations" in the GLM corresponds to in terms of patients assessed. 81% had at least 1 follow-up. No difference in baseline variables between those who completed at least 1 follow-up and those completely lost to follow-up.	Some concerns Injection frequency assessed by RBA in interview, potential for recall bias based on intervention.	Low Main outcome reported	Some concerns

Abbreviations. GLM=generalized linear model; RBA=Risk Behavior Assessment.

COHORT STUDIES (ROBINS-I)

Study Name or Author Year	Bias due to confounding	Selection bias	Bias in classification of interventions	Bias due to departures from intended interventions	Bias due to measurement of outcomes	Bias due to missing data	Bias in the selection of reported results	Overall risk of bias (Low, Moderate, Serious, Critical, No Information)
Brooner 1998;[28] Neufeld 2008[87]	Unclear Analyses controlled for baseline measures (sociodemographics, drug and psychiatric	Low Includes all who presented for treatment during timeframe.	Low Intervention classified as referral source	Low "Intervention" is referral source, so likely no overlap/departures.	Low Retention in treatment objective measurement. Drug	Low Missing data for urinalysis results only. Analyses conducted without missing	Low All prespecified results appear to be reported.	Unclear

Study Name or Author Year	Bias due to confounding	Selection bias	Bias in classification of interventions	Bias due to departures from intended interventions	Bias due to measurement of outcomes	Bias due to missing data	Bias in the selection of reported results	Overall risk of bias (Low, Moderate, Serious, Critical, No Information)
	disorders), but likely some residual confounding based on high # of differences at baseline in measured variables.		before treatment started.		use confirmed by urinalysis.	data and coding all missing as "positive."		
Hagan 2000[4]	Unclear Differences between groups in injection characteristics, adjusted for different variables in different analyses.	Low Includes sample of IDUs from several recruitment points over time.	Low Classified SSP use over follow-up period into distinct categories based on when SSP use started/stopped.	Low Classification of SSP use over time captures changes in use over the follow-up period.	Low Standard questionnaire administered by trained interviewers at all time points.	Unclear 78% completed follow-up and were included in sample, unclear if any differences between those without follow-up.	Low All prespecified results appear to be reported.	Unclear
Hartgers 1989[5]	Unclear Differences between groups at baseline in injecting and treatment variables. Includes a logistic regression controlling for some variables for borrowing outcome at first interview.	Low Includes SSP attenders and non-attenders from same geographical region during recruitment.	Low Classified SSP use over follow-up period into distinct categories based on SSP use.	Low Classification of SSP use over time captures changes in use over the follow-up period.	Low Standard questionnaire administered by trained interviewers at all time points.	High 41% completed second interview, others omitted from follow-up analysis.	Low All prespecified results appear to be reported.	High
Huo 2006[9]	Unclear Unclear baseline differences between groups, but did adjust for injecting variables, drug treatment, and age.	Unclear One SSP site had different recruitment start and follow-up duration. Adjusted for follow-up duration in analyses. Non-SSP users recruited by different people than SSP users.	Low Classified by SSP use, which was based off neighborhood. Excluded small percentage of participants in neighborhood w/o SSP who travelled to SSP.	Unclear Does not appear to account for starting/stopping SSP use over follow-up period.	Low Standard questionnaire administered by trained interviewers at all time points.	Unclear Excluded participants without at least 1 follow-up (17%), but attrition analysis showed no difference between groups in baseline injection frequency.	Low All prespecified results appear to be reported.	Unclear
Kuo 2003[26]	Unclear Baseline variables by SSP use not reported but does	Low Includes all referred to LAAM program,	Unclear All patients were enrolled in SSP but classifies use	Low Accounts for changes in SSP use by using a	Unclear Doesn't specifically describe how SSP	Unclear Describes level and management of	Low	Unclear

Study Name or Author Year	Bias due to confounding	Selection bias	Bias in classification of interventions	Bias due to departures from intended interventions	Bias due to measurement of outcomes	Bias due to missing data	Bias in the selection of reported results	Overall risk of bias (Low, Moderate, Serious, Critical, No Information)
	adjust for some demographics and other variables.	except for a small proportion who did not have SSP data.	as number of visits per month.	variable of "# SSP visits per month."	visit data was collected.	missing urinalysis data, but level and handling of missing data for other variables not described.	All prespecified results appear to be reported.	
Latkin 2006[25]	Unclear Baseline variables by SSP use not reported but does adjust for demographics and drug use variables.	High Appears that 30% without follow-up data were excluded from the study, but unclear proportion among IDUs.	Low Classified as SSP use within the past 6 months in standard survey responses.	Unclear New use of SSP or stopping SSP use during follow-up does not appear to be evaluated.	Low Standard questionnaire administered by trained interviewers at all time points.	Unclear Excluded participants without follow-up, handling of other missing data not described.	Low All prespecified results appear to be reported.	High
Marmor 2000[6]	High Unclear differences at baseline between SSP users and non-users and no adjustment for any variables.	High Excluded 45% of eligible participants without 4 interviews. Did not differ on most variables but did differ in age and use of methadone maintenance and shooting galleries.	Low Classified SSP users by use over time.	Low Classification of SSP use over time captures changes in use over the follow-up period.	Low Interviewer-administered questionnaires at all visits.	Unclear Excluded participants without 4 follow-up visits, handling of other missing data not described.	Low All prespecified results appear to be reported.	High
Monterroso 2000[7]	Unclear Unclear differences at baseline between SSP users and non-users. Unclear if SSP use analysis is adjusted.	Low Includes sample of IDUs from several recruitment points over time period.	Unclear Question around SSP use and classification of use not well described.	Unclear Mentions "consistent users" reported SSP use at 2 visits, but other classification of changes over time not described.	Low Interviewer-administered questionnaires at all visits.	High Excluded 39% of participants that did not have follow-up. Similar on most characteristics, but more likely to be homeless.	Low All prespecified results appear to be reported.	High
Schoenbaum 1996[8]	High Differences at baseline in drug use treatment, no adjustment for any	Low Includes sample of IDUs recruited over time period.	Unclear Classified as "ever" using SSP or "never" using SSP based on interviews, but	Low Classification of SSP use over time captures changes	Low Interviewer-administered questionnaires at all visits.	High For prospective analyses excluded 36%	Low All prespecified results appear to be reported.	High

Study Name or Author Year	Bias due to confounding	Selection bias	Bias in classification of interventions	Bias due to departures from intended interventions	Bias due to measurement of outcomes	Bias due to missing data	Bias in the selection of reported results	Overall risk of bias (Low, Moderate, Serious, Critical, No Information)
	confounders for outcome analyses.		intervention changed from illegal SSP to legal SSP over study period.	in use over the follow-up period.		without full follow-up data.		
Strathdee 1999;[27] Shah 2000[86]	Unclear Baseline variables by SSP use not reported but does adjust for demographics and drug use variables.	High Excluded 50% of original sample who did not inject from enrollment to post-SSP timeframe, but initial inclusion criteria required drug use from 1977.	Unclear SSP variable not well described, unclear if it is any visit over the timeframe.	Unclear SSP variable not well described, unclear if it accounts for potential changes in SSP use over time.	Low Interviewer-administered questionnaires at all visits.	Unclear Individuals who were lost to follow-up were censored. Unclear how many (says "*ie*, 10%" but unclear if this is the actual % that were censored).	Low All prespecified results appear to be reported.	High

Abbreviations. IDU=injection drug user; LAAM=levomethadyl acetate hydrochloride; SSP=syringe services program.

UNCONTROLLED PRE-POST STUDIES (ROBINS-I)

Study Name or Author Year	Bias due to confounding	Selection bias	Bias in classification of interventions	Bias due to departures from intended interventions	Bias due to measurement of outcomes	Bias due to missing data	Bias in the selection of reported results	Overall risk of bias (Low, Moderate, Serious, Critical, No Information)
Bartholomew 2021[10]	Unclear Used GEE to account for some potential confounders but did not have multiple pre-intervention measurements.	High Only included 12% of total cohort with 2 follow-up assessments, differences between baseline and follow-up groups.	Low Timepoints based on assessments completed at SSP.	Unclear Time between assessments varied and was based on SSP use.	Low Methods of data collection similar across timepoints after initial enrollment.	Unclear Excluded participants without 2 visits, level of other missing data unclear.	Low All relevant outcomes appear to be reported.	High
Cox 2000[11]	High Single initial measurement, no adjustment for time trends.	Unclear Only included 28% of those invited to participate. Unclear how many completed baseline and no	Low Timepoints based on initial and follow-up visits.	Unclear Defines follow-up at 3 months, but unclear adherence to this timing for all participants. Unclear	Low Structured questionnaires by trained interviewers at both timepoints.	Unclear Missing data appear to be excluded from analyses for individual outcomes.	Low All relevant outcomes appear to be reported.	High

Study Name or Author Year	Bias due to confounding	Selection bias	Bias in classification of interventions	Bias due to departures from intended interventions	Bias due to measurement of outcomes	Bias due to missing data	Bias in the selection of reported results	Overall risk of bias (Low, Moderate, Serious, Critical, No Information)
		follow-up and unclear differences between those included and excluded.		frequency of SSP use.				
Donoghoe 1989[12]	High Single initial measurement, no adjustment for time trends, and comparison group of non-attenders showed differences.	High Only included 6% of the initial cohort, differences between those who completed 2nd interview and those who did not.	Low Timepoints based on initial and follow-up visits.	Unclear Defines follow-up at 2-4 months, but unclear adherence to this timing for all participants. Unclear frequency of SSP use.	Low Structured questionnaires by staff at both timepoints.	Unclear Excluded participants without 2 visits, level and handling of other missing data unclear.	Low All relevant outcomes appear to be reported.	High
Iversen 2013[13]	Unclear Appears only to have adjustment for HCV incidence outcome. Accounts for time trends by creating separate groups by timeframe.	High Excluded high proportion of original sample without matching. Included 60% of the matched sample with negative HCV tests. Differences between those included and excluded.	Low Timepoints based on repeat surveys and had to be within 1-year.	Unclear Follow-up had to be within 1-year, but unclear how variable time between records was. Unclear frequency of SSP use.	Low Same survey used at all time points.	Unclear Out of original sample, excluded 17% without full data.	Low All relevant outcomes appear to be reported.	High
Patel 2018[14]	Unclear Single initial measurement, but timeframe within about 1 year.	Unclear Included 62% of original sample with at least 2 visits. Unclear differences between those included and excluded.	Low Timepoints based on visits and had to be at least 7 days apart.	Unclear Follow-up had to be at least 7 days apart, but unclear how variable time between surveys was. Unclear frequency of SSP use.	Low Structured questionnaires by staff at both timepoints.	Low Mentions missing data on only 2 participants.	Low All relevant outcomes appear to be reported.	Unclear
Schechter 1999[15]	Unclear Single initial measurement, no adjustment for time trends but injection frequency	Unclear Included 80% of original sample with 1 follow-up visit. Unclear differences between those	Low Timepoints based on initial and follow-up visits.	Unclear Unclear how timing of follow-up varied across participants. Classified frequent and	Low Structured questionnaires by staff at both timepoints.	Unclear Unclear level and handling of missing data.	Low All relevant outcomes appear to be reported.	Unclear

Study Name or Author Year	Bias due to confounding	Selection bias	Bias in classification of interventions	Bias due to departures from intended interventions	Bias due to measurement of outcomes	Bias due to missing data	Bias in the selection of reported results	Overall risk of bias (Low, Moderate, Serious, Critical, No Information)
	outcome analysis limited to post-need exchange timeframe.	included and excluded.		infrequent SSP users.				
Vertefeuille 2000[16]	Unclear Single initial measurement, no adjustment for time trends, but timeframe within 6 months.	Unclear Every 7th enrollee invited, differences between those enrolled and not enrolled in some demographics and drug use variables.	Low Timepoints based on initial and follow-up visits.	Unclear Follow-up at 6 months, but unclear frequency of SSP use.	Low Structured questionnaires by staff at both timepoints.	High Only had follow-up data for 52% of enrollees. Drug injection frequency analysis limited to those with follow-up and who were HIV positive at baseline.	Low All relevant outcomes appear to be reported.	High
Vlahov 1997[17]	Unclear Single initial measurement, no adjustment for time trends, but timeframe within 2 weeks.	Unclear Every 7th enrollee invited, differences between those enrolled and not enrolled in gender and some drug use variables.	Low Timepoints based on initial and follow-up visits.	Unclear Follow-up at 2 weeks, but unclear frequency of SSP use.	Low Structured questionnaires by staff at both timepoints.	Unclear 79% had follow-up data at 2 weeks, but difference in sharing needles between those with and without follow-up.	Low All relevant outcomes appear to be reported.	Unclear
Vogt 1998[18]	Unclear Single initial measurement, no adjustment for time trends, unclear follow-up.	Unclear Random selection of clients, but unclear how clients were randomly selected and if they differed from those not selected.	Low Timepoints based on initial and follow-up visits.	Unclear Unclear timing of follow-up visits and unclear frequency of SSP use.	Unclear Unclear if structured questionnaire used for interviews.	High Repeat interviews with 51% of participants included for follow-up analysis. Unclear differences between those with and without follow-up.	Low All relevant outcomes appear to be reported.	High

Abbreviations. GEE=generalized estimating equations; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IDU=injection drug use; SSP=syringe services program.

SYSTEMATIC REVIEWS (ROBIS)

Study Name or Author Year	Study Eligibility Criteria	Identification and Selection of Studies	Data Collection and Study Appraisal	Synthesis and Findings	Overall Risk of Bias
Jones 2010[2]	Low Reasonable and mostly clearly defined eligibility criteria. Do not explicitly describe comparator criteria but specify included study designs.	Low Multiple databases searched. Searches included both key words and controlled vocabulary, but full search syntax is not provided. Date limit of 1990 seems roughly in line with start of research on SSPs, but some studies may have been published prior to this date. Hand-searched reference lists of included studies. No grey literature searching conducted. Dual independent study selection indicated for title/abstract screening but not explicitly stated for full-text review.	Low A single reviewer abstracted data and assessed study quality, checked by another reviewer. Study quality was assessed using appropriate criteria.	Unclear Meta-analysis was not conducted due to variability between studies. Narrative synthesis did not address methodological quality; this is addressed in the discussion section, but individual quality assessments are not included.	Low
Palmateer 2022[1]	Low Reasonable and clearly defined eligibility criteria. Detailed criteria provided in Appendix.	Low Update to a 2011 review of reviews. Searches included an initial search for systematic review and additional searches for primary studies when indicated. Multiple databases searched. Conducted grey literature searches and hand searched reference lists of included records. Searches included key words and controlled vocabulary terms and full syntax is provided in the Appendix.	Unclear Dual independent study selection, data abstraction, and risk of bias assessment. Risk of bias of systematic reviews was assessed using appropriate criteria. Risk of bias of primary studies was not assessed; instead, study design was considered an indicator of quality.	Low Rated the strength of the evidence for each intervention and outcome using a framework that is clearly described in the review.	Low

Abbreviations. SSP=syringe services program.

STRENGTH OF EVIDENCE ASSESSMENTS FOR KQ1 PRIMARY STUDIES

Outcome	Studies	Study Limitations	Directness	Consistency	Precision	Rating and Summary of Evidence
Injection frequency	1 RCT,[3] 6 cohort,[4–9] and 9 pre-post[10–18] studies	Unclear to high	Direct	Consistent	Precise	Low SSP use does not appear to be associated with an increase in injection frequency.
Naloxone distribution	1 serial cross-sectional[19] and 4 cross-sectional[20–23] studies	High	Indirect	Consistent	Imprecise	Low SSP use may be associated with higher rates of carrying naloxone.
Overdose education	2 cross-sectional studies[21,24]	High	Indirect	Consistent	Imprecise	Low SSP use may be associated with receipt of overdose education.
Linkage to SUD treatment and utilization of treatment services	6 cohort[4,5,25–28] and 3 pre-post[11,16,17] studies	Unclear to high	Direct	Consistent	Precise	Low SSP use may be associated with increased treatment linkage and/or use of treatment services compared to no SSP use (or less use).
Syringe disposal	1 RCT,[29] 2 pre-post,[16,17] 11 cross-sectional,[30–40] and 7 ecological[41–47] studies	Unclear to high	Direct	Consistent	Imprecise	Low SSP use and/or presence of an SSP does not appear to be associated with an increase unsafe syringe disposal practices.
Neighborhood crime rates	2 ecological studies[48,49]	High	Direct	Inconsistent	Imprecise	Low Presence of an SSP does not appear to be associated with an increase in neighborhood crime rates.

INCLUDED SYSTEMATIC REVIEWS

Citation
Abdul-Quader AS, Feelemyer J, Modi S, et al. Effectiveness of structural-level needle/syringe programs to reduce HCV and HIV infection among people who inject drugs: A systematic review. AIDS and Behavior. 2013;17(9):2878-2892.
Aspinall EJ, Nambiar D, Goldberg DJ, et al. Are needle and syringe programmes associated with a reduction in HIV transmission among people who inject drugs: a systematic review and meta-analysis. International journal of epidemiology. 2014;43(1):235-248.
Davis SM, Daily S, Kristjansson AL, et al. Needle exchange programs for the prevention of hepatitis C virus infection in people who inject drugs: a systematic review with meta-analysis. Harm reduction journal. 2017;14(1):25.
European Centre for Disease Prevention and Control. Systematic Review on the Prevention and Control of Blood-Borne Viruses in Prison Settings.; 2018.
Fernandes RM, Cary M, Duarte G, et al. Effectiveness of needle and syringe Programmes in people who inject drugs - An overview of systematic reviews. BMC public health. 2017;17(1):309.
Johnson WD, Rivadeneira N, Adegbite AH, et al. Human Immunodeficiency Virus Prevention for People Who Use Drugs: Overview of Reviews and the ICOS of PICOS. The Journal of infectious diseases. 2020;222(S).
Jones L, Pickering L, Sumnall H, McVeigh J, Bellis MA. Optimal provision of needle and syringe programmes for injecting drug users: A systematic review. The International journal on drug policy. 2010;21(5):335-342.
Lazarus JV, Safreed-Harmon K, Hetherington KL, et al. Health Outcomes for Clients of Needle and Syringe Programs in Prisons. Epidemiologic reviews. 2018;40(1):96-104.
MacArthur GJ, van Velzen E, Palmateer N, et al. Interventions to prevent HIV and Hepatitis C in people who inject drugs: A review of reviews to assess evidence of effectiveness. International Journal of Drug Policy. 2014;25(1):34-52.
Mir MU, Akhtar F, Zhang M, Thomas NJ, Shao H. A Meta-analysis of the Association Between Needle Exchange Programs and HIV Seroconversion Among Injection Drug Users. Cureus. 2018;10(9).
Palmateer N, Hamill V, Bergenstrom A, et al. Interventions to prevent HIV and Hepatitis C among people who inject drugs: Latest evidence of effectiveness from a systematic review (2011 to 2020). The International journal on drug policy. 2022;109:103872.
Palmateer N, Kimber J, Hickman M, Hutchinson S, Rhodes T, Goldberg D. Evidence for the effectiveness of sterile injecting equipment provision in preventing hepatitis C and human immunodeficiency virus transmission among injecting drug users: A review of reviews. Addiction. 2010;105(5):844-859.
Platt L, Minozzi S, Reed J, et al. Needle syringe programmes and opioid substitution therapy for preventing hepatitis C transmission in people who inject drugs. The Cochrane database of systematic reviews. 2017;9.
Puzhko S, Eisenberg MJ, Filion KB, et al. Effectiveness of Interventions for Prevention of Common Infections Among Opioid Users: A Systematic Review of Systematic Reviews. Frontiers in public health. 2022;10:749033.
Sawangjit R, Khan TM, Chaiyakunapruk N. Effectiveness of pharmacy-based needle/syringe exchange programme for people who inject drugs: A systematic review and meta-analysis. Addiction. 2017;112(2):236-247.
Thomson K, Hillier-Brown F, Walton N, Bilaj M, Bambra C, Todd A. The effects of community pharmacy-delivered public health interventions on population health and health inequalities: A review of reviews. Preventive medicine. 2019;124:98-109.
Wright NMJ, Tompkins CNE. A review of the evidence for the effectiveness of primary prevention interventions for hepatitis C among injecting drug users. Harm reduction journal. 2006;3:27.

PEER REVIEW COMMENTS AND RESPONSES

Comment #	Reviewer #	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?			
1	1	Yes	None
2	2	Yes	None
3	3	Yes	None
4	5	Yes	None
5	6	Yes	None
6	7	Yes	None
7	8	Yes	None
Is there any indication of bias in our synthesis of the evidence?			
8	1	No	None
9	2	No	None
10	3	No	None
11	5	No	None
12	6	No	None
13	7	No	None
14	8	No	None
Are there any published or unpublished studies that we may have overlooked?			
15	1	No	
16	2	Yes - Analisa Packham, Syringe exchange programs and harm reduction: New evidence in the wake of the opioid epidemic, Journal of Public Economics, Volume 215, 2022, 104733, ISSN 0047-2727	Thank you for bringing this study to our attention. It does not meet criteria for inclusion because we did not review evidence from primary studies for HIV incidence or prevalence and drug-related mortality was not one of our pre-specified outcomes. However, this study and the response it inspired from other researchers (Lambdin 2023) is relevant to mention in the discussion section of our review as an example of how misinterpreting

Comment #	Reviewer #	Comment	Author Response
			data can lead to unjustified conclusions regarding SSP use and health outcomes.
17	3	No	None
18	5	Yes - https://doi.org/10.1007/BF02351502; https://doi.org/10.1111/jrh.12388	Thank you for highlighting these citations. The first study (Strathdee 1999) is included in our review and synthesis. The second study (Surratt 2020) is also included but was not prioritized for synthesis because it is cross-sectional and we focused on longitudinal evidence for the outcome of treatment linkages.
19	6	No	None
20	7	No	None
21	8	Yes - Packham A. Syringe exchange programs and harm reduction: New evidence in the wake of the opioid epidemic. J Public Economics 2022; 215. https://doi.org/10.1016/j.jpubeco.2022.104733. Available at https://apackham.github.io/mywebsite/opioidpaper_webcopy.pdf.	Thank you. Please see our response to comment #16.
Additional suggestions or comments can be provided below.			
22	1	Table 5: It is not correct that LAAM is no longer approved in the U.S. It is still FDA approved. It was taken off the market voluntarily by the manufacturer because of poor sales. It is the case that it is no longer approved in Europe.	Thank you for making note of this error. We have revised the text to state that LAAM is an opioid agonist no longer on the US market.
23	1	Table 5: Text in the Neufeld row seems incomplete.	Thank you for this comment. Brooner 1998 and Neufeld 2008 are 2 publications associated with a single study and the results are described in a single row. We have edited the study column to improve clarity.
24	1	Table 6: Dasgupta row. What is the “public health response?”	Thank you for this comment. We have added a footnote to specify that the public health response included establishment of the state’s first legal SSP.
25	1	Page 25, line 37: Change “along” to “alone.” Table 9, Harm Reduction row: Remove either “detox” or “detoxification.”	Thank you for making note of these errors. We have made the recommended corrections.

Comment #	Reviewer #	Comment	Author Response
26	1	Page 27, line 35: Change “justice” to “legal.” The supposed “justice” system is anything but “just.”	Thank you for this recommendation. We have revised the text to state “legal system.”
27	1	Page 28, lines 56-57: The trend toward non-injecting of fentanyl may have been short lived. Increasingly, fentanyl is showing up in powder form which is likely to be injected.	Thank you for this comment. We removed the specific reference to fentanyl and instead highlight that drug use patterns are constantly evolving, and future research could help identify best practices for SSPs to respond and maintain relevance.
28	2	Did the ESP review the extant literature for any association between SSP use and substance use? It was included in the SOW we reviewed in late Feb of this year that included the following outcomes: Drug use behaviors (e.g., sharing, borrowing, lending, reuse, or unsafe disposal of syringes; amount, speed, or frequency of use; etc); knowledge of overdose risk; naloxone distribution/use; linkage to treatment for substance use disorder, HIV/HCV, or other medical needs, or to HIV pre-exposure prophylaxis; utilization of referred services. Please note that one recent study (albeit with several methodological flaws) suggests an association between SSP implementation and increases in opioid use: "https://www.sciencedirect.com/science/article/abs/pii/S0047272722001359" Syringe exchange programs and harm reduction: New evidence in the wake of the opioid epidemic - ScienceDirect. However, the author (Analisa Packham) also notes the following: “I note that my findings imply that SEPs do little to reduce drug overdoses and may even exacerbate opioid abuse and misuse. However, the results do not suggest that SEPs are ineffective at curbing addiction for all clients. Moreover, prescription drugs, such as Buprenorphine that reduce symptoms of opiate addiction and withdrawal, or other opiate antagonists, which work in the brain to prevent opiate effects and decreases the desire to take opiate, could be one way for SEPs to mitigate clients' opioid dependence in the future.”	Thank you for your comments. The association between SSPs and substance use was partly addressed through our inclusion of injection frequency, but we did not specifically review evidence on whether use of SSPs is associated with more or less frequent drug use overall. This decision reflects the review’s focus on the role of SSPs in harm reduction. While we reviewed evidence related to naloxone distribution and overdose education, we did not include drug-related mortality as an outcome of interest. Regarding the Packham 2022 study, please see our response to comment #16.
29	2	[In second bullet of Key Findings, add ‘s’ to ‘encourage’ and ‘facilitate.’]	We have left the wording of the key findings as written, since the phrases regarding naloxone, overdose education, and treatment referral follow “may.”

Comment #	Reviewer #	Comment	Author Response
30	2	[Insert citation substantiating first statement of executive summary.]	To be consistent with our usual style, we did not include citations in the executive summary but did include citations related to increased drug use and HIV/HCV in the background section.
31	2	Please define "needs-based" SSP. Are participants required to submit used syringes to get sterile ones? If not, needs-based seems synonymous with the "distribution" model of SSPs.	Thank you for this comment. In the section on SSP models, we have revised the text to use more precise language referring to syringe distribution policies (which may be needs-based or offer a set number of syringes regardless of how many are returned) and exchange policies (which require returning used syringes).
32	2	Are SSPs that use a distribution model (no exchange) considered "more permissive?"	Thank you for this comment. Please see our response to comment #32. We have revised this section to improve clarity regarding the term “permissive.”
33	3	One area that is not discussed but may be equally important is acquired bacterial infections from using clean needles when the skin has not been cleansed using an alcohol wipe or other procedure. Cellulitis is prevalent among PWID and can lead to severe adverse outcomes. This reviewer realizes that this may not be within scope, however, due to the newest issue - fentanyl adulterated with xylazine wound issues is becoming a hot topic area.	Thank you for this comment. We agree that bacterial infections related to injection-drug use are an important outcome, but this outcome was not within the scope of this review. In the Future Research section, we added a reference to the emergence of xylazine and importance of studying best practices for SSPs to provide PWID with information and tools to reduce xylazine-specific harms.
34	5	This was a well thought out review recognizing that the research methodology is mixed. The review was concise and appropriately addressed the limitation as well as areas for future research. If I might suggest also adding improving in HIV/HCV treatment as part of linkage to care. For example, a pilot study done in 2003 points to the idea that "health services based on needle exchange may enhance access to HAART among out-of-treatment HIV-infected IDUs" (https://doi.org/10.1093/jurban/jtg053). There's another review that may be helpful, most of the references are already in the current manuscript. however, this article may provide additional references/perspectives (https://doi.org/10.1186/s13722-023-	Thank you for your comments. We included linkage to HIV treatment as an outcome but did not identify any studies that met criteria for inclusion in our synthesis. We did not include studies evaluating HIV or HCV treatment services co-located with SSPs as stand-alone interventions, which the study by Altice 2003 is an example of. We realize that the body of literature on co-located treatment services is of high interest, but reviewing this evidence

Comment #	Reviewer #	Comment	Author Response
		00394-x). Looks great and thank you for sharing and allowing me to be a part of this!	would have made the scope of this review unfeasibly large. Thank you for providing the link to the scoping review. We hand-searched this publication for relevant references as part of our search process.
35	6	This is my first review of the "Effectiveness of Syringe Service Programs: A Systematic Review". Page numbers reference the page in the PDF document. Generally, the title and corollary mentions of SSPs should be referred to as Syringe Services Programs (missing "s" in services throughout the document; cf. https://www.cdc.gov/ssp/index.html). Not sure if there was any examination of drug test strips (e.g., fentanyl test strips) in this review. Also there is frequent reference to the Office of National Drug Control Policy; however, these efforts also align with other key initiatives related to infectious disease—recommend checking with David Ross and Lorenzo McFarland on the appropriate initiatives to cite (e.g., Ending the HIV Epidemic, etc.).	Thank you for your comments. We have corrected the text to refer to Syringe Service*s* Programs (plural) throughout the document. We did not specifically examine evidence related to drug testing strips. We would have included evidence regarding drug testing strips as a component of harm reduction services provided at SSPs but did not identify such evidence. We specifically highlighted the Office of National Drug Control Policy (ONDCP) because this review was requested in part to inform ONDCP efforts. We added a sentence to the beginning of the Discussion to highlight that harm reduction is a goal of VA Offices of Mental Health and Suicide Prevention, Research and Development, and Specialty Care Services.
36	6	1. Page 9, line 10—Key Findings—"carriage" is an uncommon word used regarding naloxone—consider changing to "carrying naloxone" (also on page 10, line 32; page 30, line 50; page 31, line 14; page 40, line 14)	Thank you for this suggestion. We have revised the text to state "carrying" or "possession" of naloxone rather than "carriage."
37	6	2. Page 10—it may be helpful to clarify the difference between "Linkage to SUD treatment and utilization of treatment services" and "Additional harm reduction and referral services" (the latter seems to combine a number of services—e.g., motivation interviewing, case management, pharmacy-based SSP referral which seem to be different things). In general, these	Thank you for this comment. We reorganized the findings in this table to improve clarity and removed the row describing "Additional harm reduction and referral services." These findings are best described in the results section where additional context is provided.

Comment #	Reviewer #	Comment	Author Response
		seem like blended concepts. Not sure if it would help to better explain the universe of what is included.	
38	6	3. Page 15, lines 11-15—suggest using the term "stimulants" to refer to cocaine and psychostimulants (latter is primarily methamphetamine). Even in reference #4, psychostimulants are reported separately from cocaine (see Figure 1, https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7006a4-H.pdf)	Thank you for this suggestion. We have revised the text to use the term "stimulants."
39	6	4. Page 16, lines 5-9—not sure if you want to use the NASEN reference; https://www.nasen.org/ (over 500 SSPs).	Thank you for this suggestion. We have updated this text to reflect current data from NASEN.
40	6	5. Page 16, line 16—There is also funding from OMHSP's SUD program to fund harm reduction coordinators (should check with them about that sentence); also the "(PMOP)" should come after Program	Thank you for this comment. Because this paragraph is specific to SSPs funding, we did not expand on other VHA initiatives to promote harm reduction (of which there are many). We have corrected the placement of the PMOP acronym.
41	6	6. Page 20, line 44—based on the 95% CI that is non-significant right? Not "bordered on non-significant" but actually not statistically significant since it include 1.0	Thank you for this comment. We have corrected this statement to say "bordered on significance."
42	6	7. Page 22, line 31—superscript after 5 is underlined and doesn't need to be	Thank you for making note of this error. We have corrected this text.
43	6	8. Injection Frequency/Table 3—Bartholomew 2021 seems to indicate an increased average # of injections per day. So does Patel 2018. That is 2 of the 16 studies included in this section. Bringing this up in case it needs to be addressed to fend off potential critics.	Thank you for this comment. We added to the section on injection frequency to discuss these 2 studies specifically and provide more context for their findings.
44	6	9. Page 30, line 14—what is NEP? I don't see it defined anywhere.	Thank you for this comment. NEP refers to "needle exchange program." We have changed this reference to "NEP" to "SSP" instead to be consistent with the language of our review.
45	6	10. Page 32, lines 11-12—The confidence interval includes 1.0, is this not statistically significant? (same as Page 33, line 11)	Thank you for this comment. You are correct that this finding was not statistically significant. We have revised the text to include that point.
46	6	11. Page 32, line 30—square typo	Thank you for making note of this error. We have corrected this text.

Comment #	Reviewer #	Comment	Author Response
47	6	12. Page 32, line 49-50—this is not statistically significant right?	Thank you for this comment. You are correct that this finding was not statistically significant. In most cases, we do not comment on statistical significance in the table (regardless of whether a given finding was significant or non-significant) for the sake of brevity.
48	6	13. Page 32, line 55—this is not statistically significant right?	Please see the response to comment # 47.
49	6	14. Page 33, line 21—IVDU=Intravenous Drug Use right?	Thank you for making note of this error. We have corrected this text.
50	6	15. Page 34, line 5—this is not statistically significant right?	Please see the response to comment # 47.
51	6	16. Page 35, lines 6-7—is there an extra number in the 2nd set of parentheses?	Thank you for this comment. We have added a footnote to specify that counts were made at 2 time points pre-SSP and 3 time points post-SSP.
52	6	17. Page 36 line 37—think “along” should be “alone”; should probably be a comma after “meta-analysis” as well	Thank you for making note of these errors. We have corrected the text.
53	7	Comments to the author: This is a timely and important systematic review of the association of syringe service programs and relevant outcomes such as HIV and HCV prevalence and incidence. This report has a potential for high impact by encouraging the implementation of syringe service programs in the VA. There are several strengths to this review which include clear writing, rigorous and thorough methods, use of person-first language, and including a comprehensive group of outcomes.	Thank you for this comment.
54	7	Minor comments: 1. The statements from public health organization and professional society regarding syringe service programs are greatly appreciated. The authors may also consider adding statements from the American Academy of Addiction Psychiatry (AAAP) and American Society of Addiction Medicine (ASAM).	Thank you for this suggestion. We have added a policy statement from AAAP but could not locate a current statement from ASAM.
55	7	2. Including a description of the cost-benefits of implementing syringe service programs may strengthen the discussion, given the relatively low cost of syringes.	Thank you for this suggestion. We revised the Discussion text to specifically highlight the CDC’s statements regarding SSPs as “cost-saving.”

Comment #	Reviewer #	Comment	Author Response
56	8	1. p. 9 (pdf p. 20) – Re: Reference 24 Palmateer et al. Int J Drug Policy. 2022;109:103872. Regarding conclusion that pooled studies did not show an effect on HCV transmission, please consider commenting on whether: • Studies were appropriate for pooling, e.g., similar populations, interventions, and outcomes. • pooled studies had adequate power to detect a difference in HCV transmission. • ascertainment bias may have been present, e.g., low HCV testing rates in SSP utilizers	Thank you for your comments. We did not directly assess the quality of evidence for this outcome because we relied on the evidence synthesis conducted by the Palmateer et al. review of reviews, which we assessed to have a low overall risk of bias based on the ROBIS tool. The Palmateer et al. review in turn primarily relied on a Cochrane review and meta-analysis (Platt et al.). While we are unable to address your comments in detail, we have no reason to suspect that the conclusions reached by Palmateer et al. and Platt et al. were inappropriate.
57	8	2. p. 11 (pdf p. 22) – Primary studies Please consider comment on the following: a. Adequacy of statistical methods. Did studies have: • Pre-specified hypotheses? • Pre-specified statistical analysis plan? • Appropriate adjustments for multiple comparisons? b. Confounders. Did studies address or have data on: • population shifts in or out of the SSP's catchment? • Other factors which may have affected outcomes, e.g., public health campaigns on HIV testing, promotion of SSPs in community? • Length of time over which the study measured outcomes? c. Outcomes. Did any studies examine: • HIV or HCV testing rates • Deaths or hospitalizations due to overdoses?	Thank you for your comments. Duration of follow-up for primary studies is reported in Table 2. Statistical methods and potential risk of bias due to confounding were evaluated as part of the quality assessment of primary studies (details are located in the Appendix). HIV/HCV testing rates and overdose hospitalizations and deaths were not within the scope of this review.