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HIV/AIDS

Are needle and syringe programmes associated with a reduction in HIV transmission among people who inject drugs: a systematic review and meta-analysis

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Background Needle and syringe programmes (NSP) aim to reduce the risk of HIV by providing people who inject drugs (PWID) with sterile injecting equipment. A recent review of reviews (ROR) concluded that there was only tentative evidence to support the effectiveness of NSP in reducing HIV. We carried out a systematic review and meta-analysis to assess the association between NSP and HIV transmission.

Methods Relevant primary articles presenting data on the risk of HIV transmission associated with NSP were identified in two stages: (i) from reviews identified in two published RORs (covering the period 1980–2008); and (ii) a literature search of CINAHL, Cochrane Library, EMBASE, MEDLINE and PsychINFO for primary articles published since the most recent high quality review (covering the period 2008–12). Study results were synthesized using random-effects meta-analysis.

Results There were 12 studies comprising at least 12 000 person-years of follow-up. Exposure to NSP was associated with a reduction in HIV transmission: pooled effect size 0·66 [95% confidence interval (CI) 0·43, 1·01] across all studies, and 0·42 (95% CI 0·22, 0·81) across six higher quality studies (according to the Newcastle-Ottawa tool).

Conclusions There is evidence to support the effectiveness of NSP in reducing the transmission of HIV among PWID, although it is likely that other harm reduction interventions have also contributed to the observed reduction in HIV risk. NSP should be considered as just one component of a programme of interventions to reduce both injecting risk and other types of HIV risk behaviour.

Keywords HIV, needle-exchange programmes, people who inject drugs

Introduction

People who inject drugs (PWID) are at increased risk of HIV. Risk factors for HIV transmission among PWID include injecting risk (sharing of needles, syringes and injecting paraphernalia), as well as sexual risk behaviour.[1,2] PWID accounted for approximately 10% of new HIV diagnoses in the USA in 2009.[3] The prevalence of HIV among PWID varies depending on setting, ranging from 0.5–10% in most of Western Europe to 13–15% in the USA and Canada.[4] Strategies to reduce the risk of HIV transmission among PWID include the provision of sterile injecting equipment through needle and syringe programmes (NSP), opiate substitution therapy (OST) and sexual health promotion. NSPs now exist in more than 80 countries, although coverage is generally low.[5]

Prior reviews of the evidence concluded that the provision of NSP had led to a reduction in HIV transmission,[6,7] even though these findings were driven by a minority of the primary studies included in those reviews.[8,9] Thus, Palmateer *et al.* concluded in their review of reviews that there was only tentative evidence to support the effectiveness of NSP in reducing HIV transmission.[10] Given the appreciable number of studies identified in those reviews, the publication of new primary studies, and the ongoing importance of evaluating interventions that aim to prevent HIV, we here embarked on a separate systematic review and meta-analysis to assess the association between NSP and HIV incidence.

Methods

Literature search

Relevant primary articles presenting data on the risk of HIV transmission associated with NSP were identified in two stages: (i) from reviews identified in two published reviews of reviews (that had been conducted by the same review team);[10,11] and (ii) a literature search for primary articles published since the most recent core (high quality) review.

(i) The two reviews of reviews (RORs) examined the impact of NSP on HIV incidence (among other outcomes), and covered search periods of 1980–2007[10] and 2007–11.[11] Both RORs searched CINAHL, Cochrane Library, EMBASE, IBSS, MEDLINE and PsychINFO databases, as well as publications of key international agencies, including the European Monitoring Centre on Drugs and Drug Addiction, and the World Health Organization.[10,11]

The RORs identified five relevant reviews,[6,7,12–14] which were assigned as either core or supplementary using a tool developed by the Health Development Agency;[15] the former were regarded as reviews where the whole or part of the review was judged to be of high quality, whereas the latter were regarded as reviews that could only be included as background or contextual material. Literature searches in the core reviews covered the period 1980–2008. All primary papers mentioned in either a core or supplementary review as having examined NSP and HIV were here retrieved for further review.

(ii) A separate search for primary articles in the English language was undertaken from the date of the last core review (January 2008) up to the end of January 2012. The following databases were searched: CINAHL, Cochrane Library, EMBASE, MEDLINE and PsychINFO, using a combination of search terms, briefly summarized as 'HIV infections/transmission/seroconversion, substance abuse/dependence/injection, and harm reduction/needle exchange programmes' (Appendix 1, available as Supplementary data at *IJE* online). The reference lists of primary papers were also examined for relevant studies. A single reviewer screened article titles for relevance. Subsequently, two independent reviewers screened the identified abstracts against the PICOS criteria (Appendix 2, available as Supplementary data at *IJE* online). A third reviewer was consulted if there was disagreement between the two reviewers regarding the relevance of an abstract.

The full texts of primary articles identified through either stage (i) or stage (ii) were retrieved and assessed against the PICOS criteria. Where two or more papers were generated from the same study, the paper that provided the most recent data and/or the largest sample size was retained.

Data extraction

Primary articles meeting the selection criteria were quality assessed using the Newcastle-Ottawa (N-O) tool for cohort studies (and an amended version suitable for cross-sectional studies). The N-O tool assigns a score from one (poor quality) to nine (high quality), but there are no formal cut-off levels for study quality: therefore a score of $\geqslant 6$ was selected to denote higher quality studies, based on our reading and assessment of all the included studies. Data were extracted (to a standardized form) on the study date, location, design, selection criteria, sample size, person-years (PY) of follow-up, sex, age at recruitment, number of HIV seroconversions observed, HIV incidence in the group not exposed to NSP, HIV prevalence, definition of NSP exposure [amount of injecting equipment collected (volume), the percentage of injections where a clean needle and syringe was used (coverage), frequency of attendance at NSP or injecting during a time period when NSP was legal], definition of non-NSP exposure (relating to lower volume, coverage or attendance, or injecting during a time period when access to NSP was not legal), unadjusted/adjusted odds ratios (ORs), risk ratios (RRs) or hazard ratios (HRs) of HIV incidence associated with exposure to NSP, and covariates adjusted for. Missing data were requested from primary authors, with authors contacted twice in the case of non-response.

Data synthesis

The effect size (OR, RR or HR) and 95% confidence intervals (CIs) for HIV infection associated with exposure to NSP were extracted (or calculated) from the raw data in each article, and transformed to the natural log scale. Adjusted effect sizes were used in preference to unadjusted ones where available.

Meta-analyses were conducted in Stata 11 (StataCorp, College Station, TX, USA) using the random-effects method. The random-effects method was chosen because of the anticipated heterogeneity in populations, interventions and comparison groups used by the constituent primary studies. The existence of bias was assessed using a funnel plot.

The quality of the evidence as a whole was assessed using GRADE methodology.[16]

Sensitivity and stratified analysis

Sensitivity analyses were used to examine the effect of the following factors (determined a priori) on the pooled effect estimate: (i) outcome measurement scale (confining to studies reporting RR/HR); (ii) using the adjusted effect sizes instead of the unadjusted; (iii) study quality (confining to studies scoring $\geqslant 6$ on the N-O tool); and (iv) inclusion/exclusion of studies that raised specific issues regarding study quality.

Stratified analyses were used to investigate the following possible sources of heterogeneity: period of follow-up [group exposed to NSP followed during a later calendar period than the unexposed group (sequential follow-up), vs both groups followed concurrently (concurrent follow-up)], measurement of NSP exposure [confining to studies comparing 100% NSP coverage (clean needle and syringe used for 100% of injections) to <100% NSP coverage], geographical location (USA vs non-USA) and time period of recruitment [commenced pre-1990 vs commenced during/post-1990 (which coincided with the change from semi-official NSP provision to government programmes across the two regions (USA and Canada) where most of the primary studies were conducted].

Results

The results of the literature search are shown in Figure 1. Following the screening process, 17 primary articles were selected for consideration, of which three were excluded because they did not meet the PICOS criteria[17–19] and two were excluded because they were duplicate studies,[20,21] leaving 12 articles.

Characteristics of the studies

Of the 12 articles, one was cross-sectional,[9] 10 were cohort studies[8,22–30] and one was a case-control study[31] (Table 1). Five studies were carried out in the USA[8,9,27–29] five in Canada[22–25,31] and two in Europe.[26,30] Studies ranged in size from 226 to 2505 participants, and together totalled 12 023 individuals who had ever injected drugs and at least 11 984 PY of follow-up. Approximately 600 HIV seroconversions were observed. Six studies were initially assessed as higher quality using the N-O tool.[8,23–26,29] Subsequently, two studies[22,23] were reassessed in light of additional information from one of the included reviews[6] which reported that 'non-NSP' users in these studies actually had ready access to needles and syringes through pharmacies. This reassessment led to one study[23] being downgraded from a higher quality to a lower quality study.

Characteristics of the participants

In five studies, the analysis of NSP and HIV incidence was only conducted on a subsample of the total study participants, and the characteristics of this subsample were not described.[8,23,26–28] For the remaining studies, the percentage of male participants ranged from 60% to 81% and average age ranged from 29 to 37 years. All of the cohort studies restricted their analysis to individuals who were HIV negative at baseline.

Findings of the studies

Two of the cohort studies reported two stratified analyses, and therefore each presented two effect sizes for the association between NSP and HIV incidence.[24,29] One cohort study provided three different effect sizes [RR 1·7 (95% CI 1·0, 2·7), 1·8 (95% CI 1·1, 2·9) and 2·6 (95% CI 1·7, 4·0)]; each adjusted for a different set of variables in their analysis.[23] Our meta-analysis used the middle effect size, on the grounds that it adjusted for variables similar to those of the other studies that presented adjusted effect sizes (Table 2). In total, five cohort studies reported seven adjusted effect sizes (three reported evidence of a reduction in HIV transmission with NSP, three weak or no association and one evidence of an increase in HIV transmission).[22–25,29] and four cohort studies reported unadjusted effect sizes, all of which reported no evidence of an association.[8,26–28] One cohort study[30] reported zero seroconversions in both the intervention and control groups, and therefore was not included in the meta-analysis. The cross-sectional study reported a weak association between NSP exposure and a reduction in HIV transmission.[9] The case-control study reported a significantly increased risk of HIV transmission in the unadjusted analysis, which was non-significant in the adjusted analysis but the adjusted odds ratio was not reported.[31] Given that the adjusted result (which was unavailable) was different from the reported unadjusted result, and that sensitivity analyses excluding and including this study had little impact on effect size, this study was not included in the final meta-analyses.

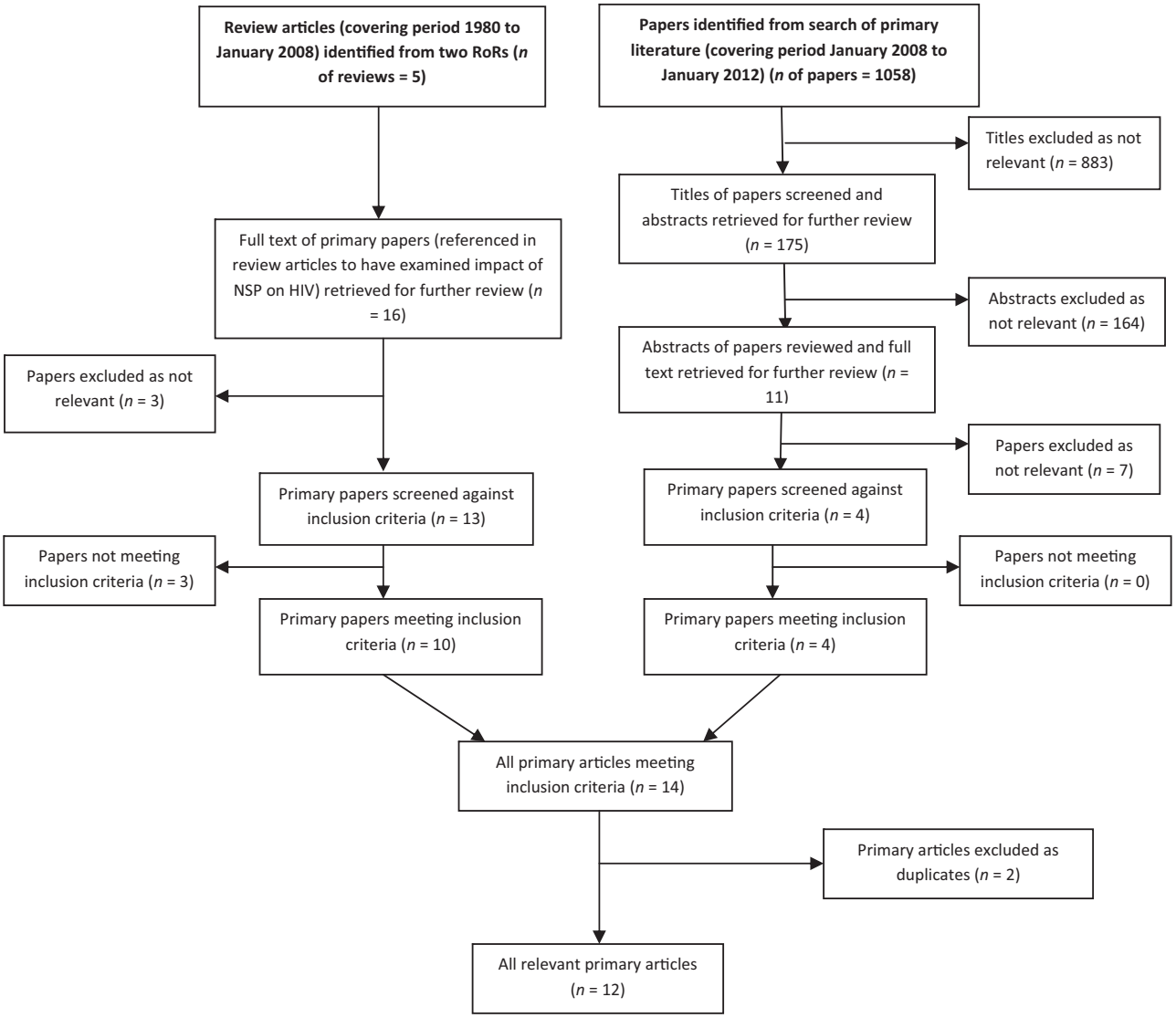

Figure 1 Literature search to identify primary articles for the systematic review

Data synthesis

The funnel plot (Appendix 3, available as Supplementary data at *IJE* online) demonstrated that studies with higher standard errors were more likely to report an association in favour of NSP exposure. Using GRADE assessment, the quality of evidence was assessed as 'Low', due to the observational nature of the primary studies and the inconsistency of effect sizes between studies (Appendix 4, available as Supplementary data at *IJE* online).

Meta-analysis generated a pooled effect estimate of 0·66 (95% CI 0·43, 1·01) $I^2 = 76\%$, of HIV transmission in individuals exposed to NSP, compared with those who were not, or were less frequently, exposed to NSP (Table 3, Figure 2).

Confining to studies reporting RR/HR, or higher quality studies, generated pooled effect estimates providing good evidence of a reduction in HIV transmission associated with NSP exposure [0·60 (95% 0·37, 0·97) $I^2 = 79\%$, and 0·42 (95% CI 0·22, 0·81 $I^2 = 80\%$, respectively], but no reduction in heterogeneity.

In the stratified analysis, studies that used sequential follow-up generated a lower pooled effect estimate (0·21, 95% CI 0·11, 0·41) than studies that used concurrent follow-up (0·98, 95% CI 0·72, 1·33), and there was a reduction in heterogeneity ($I^2 = 26\%$ and $I^2 = 48\%$, respectively). Studies that commenced recruitment during or post-1990 generated a lower pooled effect estimate (0·52, 95% CI 0·28, 0·95) than studies that commenced recruitment pre-1990 (1·05, 95% CI 0·60, 1·82). Studies comparing 100% NSP coverage with <100% NSP coverage generated a pooled effect estimate of 0·58 (95% CI 0·22, 1·57).

Table 1 Characteristics of the 12 studies identified in the systematic review, examining the association between NSP and HIV incidence in people who inject drugs (PWID)A

						Study population				Measurement of NSP exposure	
First author, year published	**Location and study years**	**Study design [N-O score]**	**Study selection criteria**	**N (person-years of follow-up)**	**Mean years of follow-up/person**	% male	Age in years at recruitment	Estimated HIV prevalence in study setting at start of study	HIV incidence among those not exposed	Exposed	Not exposed
Bruneau, 2011	Montreal, Canada, 1992–2008	Cohort [7]	PWID in previous 6 months recruited from drug detoxification, services, self-referral and street outreach. Two recruitment waves, COHORT A (recruited 2004–08) and COHORT B (recruited 1992–2001)	COHORT A 380 (612 PY) COHORT B 1757 (3828 PY)	1.61 2.18	80% 81%	33.6[b] (mean)	11% among people assessed for entry to study[b]	4.28 per 100 PY[b]	Individuals who obtained 100% of their syringes from a safe source (NSP, pharmacy, community workers) in the past 6 months	Individuals who reported that they did not obtain 100% of their syringes from a safe source in the previous six months
Kerr, 2010	Vancouver, Canada, 1998–2003	Cohort [6]	Current PWID recruited through self-referral and street outreach	1228 (NK)	NK	61%	33 (median)	NK	5.31 per 100 PY[a]	Individuals in cohort who injected during time period when access to NSP was expanded (i.e outreach, NSP distribution rather than exchange)	Individuals in cohort who injected during time period when access to NSP was more restricted (i.e. fixed sites, NSP exchange only)
Van den Berg, 2007	Amsterdam, Netherlands, 1985–2005	Cohort [7]	Ever-PWID recruited through 'open' recruitment, with separate analysis (reported here) restricted to current injectors	Subsample of 341* (2773 PY)	8.1	61%[c]	30[c] (median)	25% among people assessed for entry to study	3.07 per 100 PY	Injection drug use AND 1–100% NSP use in 6 months prior to censoring (seroconversion OR end of follow-up)	Injection drug use AND 0% NSP use in the 6 months prior to censoring (seroconversion OR end of follow-up)
Des Jarlais, 2005	New York, USA, 1990–2002	Cross-sectional [5]	PWID entering a city drug detoxification programme	2505 (N/A)	N/A	80%	37 (mean)	50% among PWID in New York	3.55 per 100 PY[d]	Injection drug use within previous 6 months, during a time period when NSP was legal	Injection drug use within previous 6 months during a time period when NSP was illegal
Valente, 2001	Baltimore, USA, 1994–97	Cohort [4]	PWID visiting an NSP at least twice during the study period	Subsample of 262 (655 PY)	2.54	72%	36–45 (mode)	29% among people assessed for entry to study	1.66 per 100 PY[a]	Above average use (measured by volume/ frequency/ duration) of NSP throughout period of follow-up	Below average use (measured by volume/ frequency/ duration) of NSP throughout period of follow-up
Monterroso, 2000	Multisite, USA, 1994–96	Cohort [6]	PWID in previous 12 months recruited from street sites, services and one correctional institute	Subsample of 1080 (540 PY)	0.65	80%[c]	38[c] (mean)	13% among people assessed for entry to study	3.76 per 100 PY[a]	'Participation' in NSP at either baseline or 6-month follow-up interview	No participation in NSP at either baseline or 6-month follow-up interview

(continued)

Table 1 Continued

First author, year published	Location and study years	Study design [N-O score]	Study selection criteria	N (person-years of follow-up)	Mean years of follow-up/person	Study population				Measurement of NSP exposure	
						% male	Age in years at recruitment	Estimated HIV prevalence in study setting at start of study	HIV incidence among those not exposed	Exposed	Not exposed
Mannson, 2000	Malmo, Sweden, 1990–93	Cohort [7]	PWID 20 years of age and above who attended a syringe exchange programme at least once during the study enrolment period	515 (1296 PY)	2.52	75%	33 (median)	2% among people assessed for entry to study	0	Attendance at NSP during study period	Non-attendance at NSP during study period
Schechter, 1999	Vancouver, Canada, 1996–98	Cohort [5]	PWID in previous 1 month recruited through self-referral and street outreach	694 (768 PY)	1.11	68%	32 (median)	NK	5.31 per 100 PY[a]	Users of NSP at least once weekly at study entry	Less frequent or no use of NSP at study entry
Bruneau, 1997	Montreal, Canada, 1988–94	Cohort [5]	PWID in previous 6 months recruited from drug detoxification, services, self-referral and street outreach	Subsample of 974 (NK)	1.79	80%[c]	32[c] (median)	NK	3.1 per 100 PY	'Participation' in NSP during previous 6 months at study entry	No participation in NSP during previous 6 months at study entry
Patrick, 1997	Vancouver, Canada, 1994	Case-control [N/A]	PWID in past 18 months, recruited from services, community outreach and self-referral	226 (NA)	N/A	67%	35 (mean)	7% among PWID in Vancouver tested during time period of study	NA	Daily to weekly use of NSP during 18 month inter-test interval	Monthly or less frequent NSP use during 18-month inter-test interval
Schoenbaum, 1996	New York, USA, 1985–93	Cohort [5]	PWID (any drug injection during study period) entering methadone treatment	Subsample of 431[a] (1813 PY)*	4.20	60%	29 (median)	52% among people assessed for entry to study	1.69 per 100 PY	Ever users of NSP during study period	Never users of NSP during study period
Des Jarlais 1996a	Multisite, USA, 1988–94	Cohort [8]	PWID recruited from NSP and street outreach	1309 (736 PY)	0.58	65%–78%	30–39 (mode)	NK	6.23 per 100 PY	Use of NSP at least 3 months prior to study visit with HIV-negative test, and continued use throughout time at risk	No legal access to NSP during entire period at risk
Des Jarlais 1996b	New York, USA, 1992–95	Cohort [8]	PWID recruited from a methadone programme and community outreach	321 (259 PY)	0.83	80%	40–49 (mode)	50% among injecting drug users in New York	5.26 per 100 PY	Use of NSP at least 3 months prior to study visit with HIV-negative test, and continued use throughout time at risk	No use of NSP during entire period at risk

N-O Newcastle Ottawa; N/A, not applicable; NK, not known and not available from the authors of the study.
[a]Estimated.
[b]Cohort A and Cohort B combined.
[c]Of full study sample rather than subsample of interest.
[d]HIV incidence measured using validated serological marker for new HIV infection (STARHS).

Table 2 Risk of HIV associated with NSP use among 12 studies identified in the systematic review

First author, year published	Outcome in analyses	'Definition' of NSP	Time period studied	Number of HIV seroconversions per persons or person years (PY)	Measure of effect (95% confidence interval)		
					Unadjusted	Adjusted	Covariateas included in adjusted model
Bruneau, 2011a	HR of HIV incidence	Less than 100% syringes from safe source	2004–08			(a) 1.00	Age, gender, unstable housing, cocaine/heroin use, sharing with someone know to be HIV positive, booting, sex with HIV-positive individual (both models)
		100% syringes from safe source	2004–08	53/1237 PY[a]	1.00	0.18 (0.04–0.89)	
Bruneau, 2011b		Less than 100% syringes from safe source	1992–2001	90/2418 Y[a]	0.88 (0.63, 1.24)[a]	(b) 1.00	
		100% syringes from safe source	1992–2001			1.05 (0.73–1.51)	
Kerr, 2010	HR of HIV incidence	Restricted access to NSP	1998–2000	27 cases ◊	–	1.00	Gender, aboriginal ancestry, daily heroin/cocaine injection, unprotected sex
		Expanded access NSP	2001–03	19 cases ◊		0.13 (0.06–0.31)	
Van den Berg, 2007	HR of HIV incidence	0% NSP coverage	1985–2005	26/847 PY	1.00	–	
		1–100% NSP coverage[b]	1985–2005	46/1579 PY	0.91 (0.57–1.45)		
Des Jarlais, 2005	RR of HIV incidence	No access to legal NSP	1990–92	5/392 persons	1.00	–	–
		Access to legal NSP	1993–2002	10/2098 persons	0.38 (0.13–1.10)		
Valente, 2001	OR of HIV incidence	Below average use of NSP	1994–97	7/155 persons	1.00	–	–
		Above average use of NSP	1994–97	5/102 persons	1.18 (0.65–2.15)		
Monterroso, 2000	RR of HIV incidence	Participation at neither study visit	1994–96	9/368 persons	1.00	–	–
		Participation at either study visit	1994–96	10/712 persons	0.57 (0.24–1.40)		
Mannson, 2000	No events observed	Attendance at NSP during study period	1990–93	In total: 0/1296 PY	–	–	–
		Non-attendance at NSP during study period	1990–93				
Schechter, 1999	RR of HIV incidence	Non-users of NSP	1996–98	17/289 persons	1.00	1.00	Injecting frequency, cocaine injection, needing help injecting, and living circumstances
		NSP use at least once weekly	1996–1998	47/405 persons	1.97 (1.16–3.36)	1.20 (0.60–2.20)	

(continued)

Table 2 Continued

First author, year published	Outcome in analyses	'Definition' of NSP	Time period studied	Number of HIV seroconversions per persons or person years (PY)	Measure of effect (95% confidence interval)		
					Unadjusted	Adjusted	Covariateas included in adjusted model
Bruneau, 1997	HR of HIV incidence	Non users of NSP	1988–94	In total: 89/974 persons	–	1.00	Age, entry period, gender, language, borrowing drug equipment from an HIV-positive individual, drug use during casual encounters, source of injecting equipment
		Exclusive users of NSP	1988–94			1.8 (1.1–2.9)	
Patrick, 1997	OR of HIV incidence	Monthly or less users of NSP Daily to weekly users of NSP	1995	12/67 persons	1.00	'Not significant'[c]	Borrowing syringes, sex with opposite gender, unstable housing, THC use, frequency of injecting
			95	58/159 persons	2.63 (1.30–5.32)		
Schoenbaum, 1996	HR of HIV incidence	Never users of NSP	1985–93	23/1360 PY ◊	1.00	–	–
		Ever users of NSP	1985–93	8/453 PY ◊	1.05 (0.47–2.32)		
Des Jarlais, 1996a	HR of HIV incidence	No access to NSP during time at risk.	1988–91	24/546 PY	1.00	(a) 1.00	Age, gender, race, and injecting frequency
		Consistent NSP use during time at risk	1992–94	3/190 PY	0.25 (0.08–0.82)	0.25 (0.07–0.91)	
Des Jarlais, 1996b	HR of HIV incidence	No NSP use during time at risk	1992–95	6/114 PY	1.00	(b) 1.00	Age, gender, race, and injecting frequency
		Consistent NSP use during time at risk	1992–95	2/145 PY	0.26 (0.05–1.28)	0.25 (0.05–1.43)	

[a]Combined for cohorts A and B.
[b]Subgroup of van den Berg compared 0% NSP coverage with 100% NSP coverage; effect size 0.95 (95% CI 0.59, 1.52).
[c]The adjusted effect size was not reported and was not available from the authors of the study.
NK, not known and not available from the authors of the study; ◊, approximation; THC, Tetrahydrocannabinol

Table 3 Pooled effect size estimates of the risk of HIV among PWID exposed to NSP compared with those less exposed to NSP: results of the meta-analyses

	Inclusion of studies in meta-analysis		Studies included	No. of effect sizes/ studies	Pooled effect estimate (95% CI)[a]	Heterogeneity (I^2)	Heterogeneity, *P*-value
All studies			Bruneau 2011a, Bruneau 2011b, Kerr 2010, Van den Berg 2007, Des Jarlais 2005, Valente 2001, Monterroso 2000, Schechter 1999, Bruneau 1997, Schoenbaum 1996, Des Jarlais 1996a, Des Jarlais 1996b	12/10	0.66 (0.43, 1.01)	76%	<0.001
Sensitivity analysis	Confining to studies reporting relative risks or hazard ratios		Bruneau 2011, Bruneau 2011b, Kerr 2010, Van den Berg 2007, Des Jarlais 2005, Monterroso 2000, Schechter 1999, Bruneau 1997, Schoenbaum 1996, Des Jarlais 1996a, Des Jarlais 1996b	11/9	**0.60 (0.37, 0.97)**	79%	<0.001
	Confining to studies reporting adjusted outcome measures		Bruneau 2011a, Bruneau 2011b, Kerr 2010, Schechter 1999, Bruneau 1997, Des Jarlais 1996a, Des Jarlais 1996b	7/5	0.52 (0.25, 1.09)	85%	<0.001
	Confining to studies scoring ⩾6 on the N-O quality scale		Bruneau 2011a, Bruneau 2011b, Kerr 2010, Van den Berg 2007, Monterroso 2000, Des Jarlais 1996a, Des Jarlais 1996b	7/5	**0.42 (0.22, 0.81)**	80%	<0.001
	All studies, including Patrick 1997[b]		Bruneau 201 a, Bruneau 2011b, Kerr 2010, Van den Berg 2007, Des Jarlais 2005, Valente 2001, Monterroso 2000, Schechter 1999, Bruneau 1997, Patrick 1997, Schoenbaum 1996, des Jarlais 1996a, des Jarlais 1996b	13/11	**0.74 (0.48, 1.13)**	78%	<0.001
Stratified analysis	Follow-up	Group exposed to NSP and group not exposed to NSP followed sequentially	Kerr 2010, Des Jarlais 2005, Des Jarlais 1996a	3/3	**0.21 (0.11, 0.41)**	26%	0.26
		Group exposed to NSP and group not exposed to NSP followed concurrently	Bruneau 2011a, Bruneau 2011b, Van den Berg 2007, Valente 2001, Monterroso 2000, Schechter 1999, Bruneau 1997, Schoenbaum 1996, Des Jarlais 1996b	9/8	0.98 (0.72, 1.33)	48%	0.05

(continued)

Table 3 Continued

Inclusion of studies in meta-analysis		Studies included	No. of effect sizes/ studies	Pooled effect estimate (95% CI)[a]	Heterogeneity (I^2)	Heterogeneity, *P*-value
Time period of recruitment	Recruitment to study commenced during/ post 1990	Bruneau 2011a, Bruneau 2011b, Kerr 2010, Des Jarlais 2005, Valente 2001, Monterroso 2000, Schechter 1999, Des Jarlais 1996b	8/7	**0.52 (0.28, 0.95)**	80%	<0.001
	Recruitment to study commenced pre 1990	Van den Berg 2007, Schoenbaum 1996, Des Jarlais 1996a, Bruneau 1997	4/4	1.05 (0.60, 1.82)	61%	0.05
Measurement of NSP	Compares 100% NSP coverage with <100% coverage	Bruneau 2011a, Bruneau 2011b, Van den Berg 2007	3/2	0.58 (0.22, 1.57)	89%	<0.001
Geographical location	USA	Des Jarlais 2005, Valente 2001, Monterroso 2000, Schoenbaum 1996, Des Jarlais 1996a, Des Jarlais 1996b	6/5	0.62 (0.36, 1.05)	47%	0.09
	Non-USA	Bruneau 2011a, Bruneau 2011b, Kerr 2010, Van den Berg 2007, Schechter 1999, Bruneau 1997	6/5	0.69 (0.36, 1.34)	87%	<0.001

[a]Weights are derived from random-effects meta-analysis.
[b]Sensitivity analysis carried out including/excluding Patrick 1997, due to the difference between the unadjusted and the (unavailable) adjusted effect size.

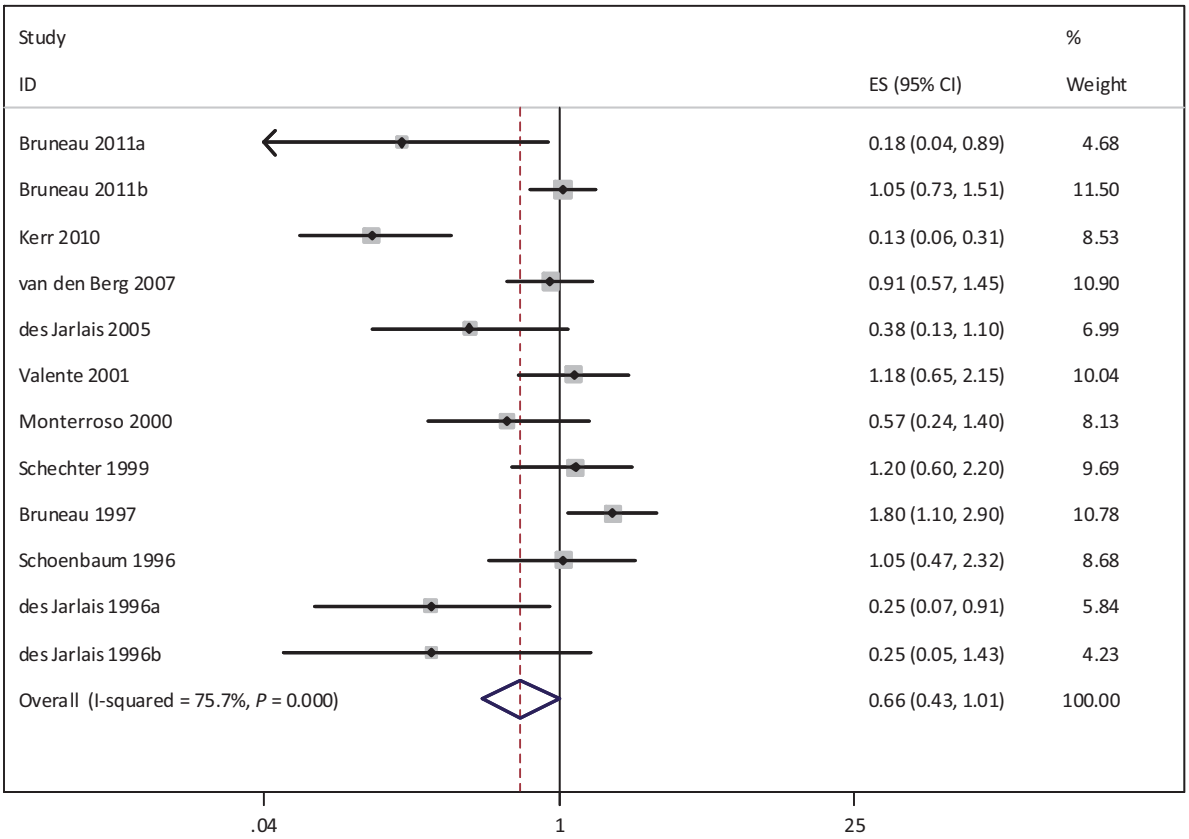

Figure 2 Forest plot of studies examining the association between NSP exposure and HIV incidence
Note: Weights are from random-effects analysis using the method of DerSimonian & Laird, with the estimate of heterogeneity being taken from the Mantel-Haenszel model. ES; effect size

Discussion

There was evidence for the effectiveness of NSP in reducing HIV transmission, across 12 studies comprising at least 12 000 PY of follow-up. Our results strengthen and build on the findings of the reviews by Tilson *et al.* and Palmateer *et al.*, which reported that there was tentative evidence to support the effectiveness of NSP in HIV prevention.[10,14]

There was a number of limitations to our review. We relied on previous reviews of the literature to identify primary studies prior to 2008, and did not include studies in languages other than English; therefore some primary studies may have been missed. There was some evidence of publication bias, with larger standard errors observed in studies that reported a protective association between NSP and HIV. However, some of the larger standard errors were generated from large sample sizes that had shorter (less than 1 year) periods of follow-up (and therefore a lower number of PY).[8,29] Because these studies quoted hazard ratios, the confidence intervals around their estimates were wider than if the corresponding relative risks had been calculated. The use of a funnel plot where different types of outcome measure (OR, HR, RR) have been calculated may therefore be somewhat misleading. Due to the small number of studies in the review, and the results of the sensitivity analyses, it was considered that the different outcome measures should still be combined in the meta-analyses.

The overall quality of the evidence in the review was graded as low, due to the considerable limitations of the constituent primary studies. The design of studies evaluating the impact of NSP on HIV is inherently difficult, given the many factors (the existing burden of HIV in the population of interest, the mode of HIV transmission, accessibility and uptake of preventative measures and the frequency of injecting equipment sharing with an HIV-positive individual with a transmissible viral load) that affect the risk of HIV seroconversion. Although randomization would normally address some of these issues, this would not be possible in the evaluation of NSP, given that its effectiveness in preventing injecting risk behaviour has already been demonstrated.[10] However, some aspects of study design that could have been considered; such as measurement of NSP coverage over the time period at risk, adjusting for sexual transmission of HIV, selection of a non-exposed group that were genuinely non-(rather than less frequent) users of NSP and reporting the number

of HIV seroconversions per PY of follow-up for both exposed and non-exposed groups, were only addressed by a small number of the primary studies. Further, given that HIV seroconversion was a relatively rare event, most studies were likely to be underpowered to detect a meaningful difference in HIV seroconversion between users and non-users of NSP; for example, detecting a relative risk of 0.7 with 80% power would require around 3000 PY of follow-up, if incidence of HIV in the non-exposed group was (as in most of the included studies) around five cases per 100 PY. It should be noted however, that many of the primary studies examined HIV incidence as a secondary outcome, and therefore could not be expected to design their study on the basis of examining HIV incidence alone.

We attempted to control for some of these issues of study quality in the sensitivity and stratified analyses. Restricting to studies where NSP exposure was defined as '100% NSP coverage' suggested a protective effect of NSP (pooled effect estimate 0·58, 95% CI 0·22, 1·57), as did restricting to higher quality studies (pooled effect estimate 0·42, 95% CI 0·22, 0·81). However, even the higher quality studies did not meet the 'gold standard' of a randomized controlled trial, and quality scores are inherently subjective. Studies that commenced recruitment during/after 1990 suggested a protective effect of NSP, whereas studies that commenced recruitment prior to 1990 showed no association. This may reflect improvements in NSP delivery (for example, changes from needle exchange to distribution, and lifting caps on the amount of equipment distributed) as harm reduction services evolved. However, given that the stratified analyses could only adjust for single variables, this result could merely be due to confounding.

In subgroup analysis, studies using successive follow-up suggested a protective association between NSP and HIV, whereas studies using concurrent follow-up found no association, and the confidence intervals around these two estimates did not overlap. Two of the studies that used successive follow-up periods used changes in the legal status of NSP to perform 'natural experiments' comparing HIV transmission before and after changes in policy.[9,25] Such studies invite regression of the mean, given that NSP policy may have been changed as a direct result of high HIV incidence rates among PWID in these areas. In addition, the time period covered by these studies (1990–2003) coincided with the introduction or expansion of other programmes that may have played a role in HIV prevention, including sexual health promotion, anti-retroviral therapy[32] and OST.[26] These interventions were not adjusted for in the studies that used successive follow-up (although Des Jarlais *et al.* corrected for injecting frequency, which was likely to be associated with OST), and therefore it is possible that it was these interventions (rather than NSP) that contributed to the observed reductions in HIV.

There was considerable residual between-study heterogeneity that could not be accounted for by the variables investigated in the stratified analyses. This is frequently observed across studies of public health programmes, where outcomes tend to be programme- and context-dependent, and there may be numerous unmeasured (or unmeasurable) variables.[33] The studies in our review covered a variety of countries, recruitment sites and models of NSP provision. A stratified analysis by geographical location had little impact on heterogeneity, but it was not possible to stratify by any of the other variables, mainly due to a lack of available information in the primary studies.

Conclusion

The results of our study suggest there is evidence to support the effectiveness of NSP in reducing HIV transmission, although the quality of this evidence was graded as low. In the context of NSP having been a cornerstone of harm reduction policy for over two decades, randomized trials would be difficult to perform for ethical and practical reasons, and it is questionable whether further observational studies would shed additional insights on the effectiveness of NSP in preventing HIV. Given the reductions in HIV risk over successive calendar periods observed in our review, it is likely that other harm reduction interventions have also made significant contributions to reductions in HIV. NSP should be scaled up (especially in areas with high rates of HIV transmission among PWID), but should be considered as just one component of a comprehensive programme of interventions to reduce both injecting risk and other types of HIV risk behaviour.

Supplementary Data

Supplementary data are available at *IJE* online.

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Conflict of interest: None declared.

KEY MESSAGES

- There was evidence for the effectiveness of NSP in preventing HIV transmission across 12 studies comprising at least 12 000 PY of follow-up.
- The protective association between NSP and HIV was largely driven by studies that used successive rather than concurrent follow-up, suggesting that other interventions that were introduced over the same time period (including sexual health promotion, anti-retroviral therapy and OST) may have contributed to reductions in HIV.
- NSP should be scaled up, but should be considered as just one component of a comprehensive programme of interventions to reduce both injecting risk and other types of HIV risk behaviour.

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