Appendix 1: Supplementary tables [posted as supplied by author]

Table A. Medline search strategies used to identify relevant articles

	Search 1[a]	**Search 2**
1	*HIV infections/pc (MESH)	exp HIV Infections/di, ep, pc, tm [Diagnosis, Epidemiology, Prevention & Control, Transmission]
2	(HIV or human immunodeficiency virus)	exp acquired immunodeficiency syndrome/pc, tm, di, ep
3	Transmission.tw.	exp HIV Seropositivity/di, ep, pc, tm [Diagnosis, Epidemiology, Prevention & Control, Transmission]
4	Seroconver$.tw.	(HIV adj2 seroconver$).ti,ab.
5	1 or (2 and 3) or (2 and 4)	(HIV adj2 transmission).ti,ab.
6	*substance abuse, intravenous/	1 or 2 or 3 or 4 or 5
7	(substance$ or drug$).tw.	exp Substance Abuse, Intravenous/
8	(abuse$ or depend$ or use$ or misus$ or addict$).tw.	((inject$ or intravenous) adj (drug$ or substanc$)).ti,ab.
9	(inject$ or intravenous).tw.	((abuse$ or depend$ or use$ or misuse$ or addict$) adj2 (opiat$ or opioid$ or heroin$ or morphin$ or morfin$ or narcot$)).ti,ab.
10	6 or (7 and 8) or (7 and 9)	exp opioid-related disorders/
11	*methadone/	7 or 8 or 9 or 10
12	*buprenorphine/	exp Cohort Studies/
13	(substitution or maintenance).ti,ab.	exp Longitudinal Studies/
14	(substitution or maintenance).mp.	(prospective or longitudinal or cohort).ti,ab.
15	11 or 12 or 13 or 14	12 or 13 or 14
16	5 and 10 and 15	6 and 11 and 15

[a] Search strategies were adapted for EMBASE and PsychINFO as required.

Table B. Risk of bias criteria for randomised controlled trials, controlled clinical trials and prospective observational studies

Item	Judgment	Description
1. Random sequence generation (selection bias)	Low risk	• The investigators describe a random component in the sequence generation process such as: random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization
	High risk	• The investigators describe a non-random component in the sequence generation process such as: odd or even date of birth; date (or day) of admission; hospital or clinic record number; alternation; judgement of the clinician; results of a laboratory test or a series of tests; availability of the intervention • Observational prospective study
	Unclear risk	• Insufficient information to permit judgement of low or high risk
2. Allocation concealment (selection bias)	Low risk	• Investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based, and pharmacy-controlled, randomization); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
	High risk	• Investigators enrolling participants could possibly foresee assignments because one of the following method was used: open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. if envelopes were unsealed or non opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure. • Observational prospective study
	Unclear risk	• Insufficient information to permit judgement of low or high risk. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement.
3. Blinding of participants and providers (performance bias)	Low risk	• Blinding of participants and providers and unlikely that the blinding could have been broken; • The outcome is unlikely to be influenced by lack of blinding.

	High risk	• No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding • Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear risk	• Insufficient information to permit judgement of low or high risk
4.Blinding of outcome assessor (detection bias)	Low risk	• No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding (i.e. objective outcome, record linkage) • Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk	• No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding (i.e. self report) • Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding (i.e. self report)
	Unclear risk	• Insufficient information to permit judgement of low or high risk
5. Incomplete outcome data (attrition bias)	Low risk	• No missing outcome data • Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias) • Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size • Missing data have been imputed using appropriate methods • All randomized patients are reported/analyzed in the group they were allocated to by randomization irrespective of non-compliance and co-interventions (intention to treat)

	High risk	• Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size • 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization
	Unclear risk	• Insufficient information to permit judgement of low or high risk (e.g. number randomized not stated, no reasons for missing data provided; number of drop out not reported for each group)
6. Free of other bias: Comparability of cohorts for baseline characteristics and outcome measures on the basis of the design or analysis	Low risk	• Exposed and non exposed individuals are matched in the design for most important confounding factors • Authors demonstrated balance between group for the confounders • Analysis are adjusted for most important confounding factors and imbalance • Randomised controlled trial
	High risk	• No matching or no adjustment for most important confounding factor
	Unclear risk	• No information about comparability of cohort
7. Free of other bias: Selection of the non exposed cohort	Low risk	• The sample has been drawn from the same community as the exposed cohort
	High risk	• The sample has been drawn from a different source
	Unclear risk	• No description of the derivation of the non exposed cohort
8. Free of other bias: protection against contamination	Low risk	• Allocation was by community, institution or practice and it is unlikely that the control group received the intervention.
	High risk	• It is likely that the control group received the intervention
	Unclear risk	• It is possible that communication between intervention and control groups could have occurred
9. Ascertainment of exposure	Low risk	• Information in the study was obtained from a secure record (e.g. clinical records or structured interview)
	High risk	• Self report

Unclear risk	•	No description

The risk of bias tool of individual observational studies was assessed using criteria drawn from the Newcastle-Ottawa Scale and the Cochrane Effective Practice and Organisation of Care Group. Risk of bias tables were operationalized to be used both for the assessment of RCTs, CCTs, and prospective observational studies according to the criteria recommended by the Cochrane Drugs and Alcohol Review Group.

Table C. Attrition rates in the included studies.

Study	Risk of attrition bias	Included at entry (n)	Included in follow up (n)	Lost to follow up (%)	Notes
Bruneau et al, unpublished	High	2074	1374	33.7	Published paper from the same cohort (Bruneau et al 2011) stated those without follow up visit were slightly younger, more likely to have used heroin >30 times in the past month; and less likely to have visited a needle/syringe programme in the previous 6 months
Chitwood et al, 1995	Low	Cases: 23 Controls: 76	Cases: 21 Controls: 68	Cases: 8.7 Controls: 10.5 Total: 10.1	Controls lost to follow up were more likely to be African American but there was no difference by age or gender. Other differences not known
Deren et al, unpublished	High	NY: 372 PR: 236	NY: 154 PR: 143	NY: 58.6[a] PR: 39.4	Data relate to attrition at 36 months
Judd et al, unpublished	High	410	273	33.4	Insufficient data on differences between those remaining in study and those lost to follow-up
Kerr et al, 2006	Low	1223	1013	17.2	No data provided regarding differences between those remaining in study and those lost to follow up
Metzger et al, 1993	Low	IT: 152[b] OT: 103	IT: 138 OT: 88	IT: 9.3% OT: 15%	Individuals lost to follow-up were more likely to be engaging in risk behaviours such as needle sharing and unsafe sex but these differences did not differ between the in treatment and out of treatment cohorts
Nelson et al, 2002	High	2097	1532	27.0	Cohort replenished with n=338 PWID to account for loss to follow up during study
Suntharasamai et al, 2009	Low	2546	2295	9.9	Data relate to attrition at 36 months
Van den Berg et	High	1640	1276		Data relate to those with ≥2 visits. Those with >1 follow up

al, 2007				22.2	visit were more likely to be older, male and HIV positive
Vanichseni et al, 2001	Unclear	1209	1124	7.0 - ≥ 1 visit 18.1 – 12mo 37.8 – 24mo 52.4 – 36mo	Figures for follow up at 12, 24 and 36 months relate to attendance at specific follow up visits
Williams et al, 1992	High	98	98	0.0	Wide range in follow up period (7-89 months). No data regarding difference between those lost to follow up over duration of study period
Moss et al, 1994	High	2351	749	68.1	Data relate to individuals with at least one follow-up visit
Ruan et al, 2007	High	333	234 – year 1 252 – year 2 229 – year 3	29.7 – year 1 24.3 – year 2 31.2 – year 3	
Serpelloni et al, 1994	Unclear	952	40 cases 40 controls		Nested case control study
Zangerle et al, 1992	High	146	102	30.1	Data relate to those re-tested for HIV at least once

[a] NY: New York cohort; PR: Puerto Rico cohort.

[b] IT: in treatment cohort; OT: out of treatment cohort

Table D. Univariable meta-regression analyses

Variable	Number of studies	Univariable rate ratio (95% CI)	Ratio of rate ratios (95% CI)	P value	$\tau^{2\,(a)}$
Geographic region					
North America	6	0.38 (0.23-0.65)	1.00 (ref)		
Europe	2	0.40 (0.22-0.71)	1.18 (0.32-4.31)		
SE Asia	1	0.78 (0.58-1.05)	2.12 (0.52-8.59)	0.47	0.22
Site of recruitment					
Clinic/outreach	4	0.38 (0.19-0.77)	1.00 (ref)		
Community/outreach	4	0.58 (0.40-0.83)	1.32 (0.45-3.84)		
Clinic	1	0.16 (0.02-1.30)	0.40 (0.02-7.84)	0.59	0.20
Duration of OST exposure					
Follow up (max 89 months)	1	0.16 (0.02-1.30)	1.00 (ref)		
12-18 months	2	0.21 (0. 09-0.50)	1.25 (0.06-24.13)		
6 months	6	0.55 (0.38-0.79)	3.38 (0.22-51.82)	0.18	0.09
Monetary incentive					
No incentive	3	0.42 (0.27-0.64)	1.00 (ref)		
Incentive	6	0.48 (0.29-0.80)	1.19 (0.42-3.38)	0.70	0.19
Females (%)					
10% increase	8	---	0.82 (0.60-1.13)	0.18	0.06
Ethnic minority (%)					
10% increase	6	---	1.00 (0.79-1.26)	0.99	0.23

[a] τ^2 from null meta-regression 0.154

Table E. Data regarding HIV incidence and estimate of effect of methadone detoxification treatment in relation to HIV transmission among people who inject drugs.

	Exposure variable	**HIV seroconversions / person years**	**HIV incidence per 100 py (95% CI)**	**Rate ratio (95% CI)**
Vanichseni et al 2001	45-day detoxification in past 4 months; Methadone maintenance treatment	Detox: 106/1730.6 MMT: 24/488.3	6.1 (5.0-7.4) 4.9 (3.1-7.3)	1.2 (0.7-1.8)
Nelson et al 2002	Detoxification in past 6 months (yes/no)	Yes: 33/778 No: 243/8033	Yes: 4.24[1] No: 3.03	1.4 (0.97-2.02)
Suntharasamai et al 2009	45-day methadone detoxification in past 6 months (yes/no)	Yes: 89/1666 No: 121/5130	Yes: 5.3 (4.3-6.6) No: 2.4 (2.0-2.8)	2.4 (1.8-3.3)
Bruneau J (unpublished)	Methadone detoxification in past 6 months (yes/no)	Data not available	Data not available	1.62 (0.38-6.94)

[1] 95% confidence intervals were not reported.

Table F. List of studies not eligible for inclusion among studies for which authors were contacted as part of search 2.

Author (year)	Title and publication details	Reason for exclusion
Solomon (2010)	Low incidences of human immunodeficiency virus and hepatitis C virus infection and declining risk behaviors in a cohort of injection drug users in Chennai, India. American Journal of Epidemiology 172(11):1259-1267	OST exposure among <1% of cohort
Quan (2011)	Mortality and HIV transmission among male Vietnamese injection drug users. [References]. Addiction 106(3):583-589	OST not implemented
Wei (2006)	HIV incidence, retention, and changes of high-risk behaviors among rural injection drug users in Guangxi, China. Substance Abuse 27(4):53-61	Data regarding OST exposure not collected
Longshore (1996)	HIV incidence among injection drug users. Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology 11(3):308-309	Data regarding OST exposure not collected
Widell (2009)	Continued heavy transmission of HCV in a needle exchange program that is associated with minimal tranmission of HIV. A nine year longitudinal cohort study. International Liver Congress 2009, 44th Annual Meeting of the European Association for the Study of the Liver Copenhagen Denmark	Data regarding OST exposure not collected (large proportion also non-opiate injectors)
Des Jarlais (2000)	HIV incidence among injection drug users in New York City, 1992-1997: Evidence for a declining epidemic. American Journal of Public Health 90 (3) (pp 352-359	All participants received treatment
Broers (1998)	Prevalence and incidence rate of HIV, hepatitis B and C among drug users on methadone maintenance treatment in Geneva between 1988 and 1995. AIDS 12(15):2059-2066	All participants received treatment
Hankins (2002)	Continuing HIV transmission among injection drug users in Eastern Central Canada: The SurvUDI study, 1995 to 2000. Journal of Acquired Immune Deficiency Syndromes 30(5):514-521	Majority of participants not opiate injectors
Monterroso (2000)	Prevention of HIV infection in street-recruited injection drug users. The Collaborative Injection Drug User Study (CIDUS). Journal of Acquired Immune Deficiency Syndromes: JAIDS 2000; 25(1):63-70	Large proportion of participants not opiate-only injectors
Tovanabutra (2004)	The changing molecular epidemiology of HIV type 1 among northern Thai drug users, 1999 to 2002. AIDS Research & Human Retroviruses 20 (5):465-475, 2004	No details provided
Sabbatini (2001)	Recent trends in the HIV epidemic among injecting drug users in Northern Italy, 1993-1999. AIDS 15 (16):2181-2185	No details provided
Vaccher (1989)	Incidence of seroconversion and progression of HIV disease among intravenous drug abusers. Journal of Acquired Immune Deficiency Syndromes 2 (4):414-415	No details provided
Ouellet (2000)	Prevalence and incidence of HIV among out-of-treatment injecting drug users, Chicago 1994-1996. Journal of Acquired Immune Deficiency Syndromes: JAIDS 25 (5):443-450	No details provided

Table G. List of excluded studies regarding non-methadone OST or different modalities of OST.

Author (year)	Title and publication details
Duburcq (2000)	Suivi a 2 ans d'une cohorte de patients sous buprenorphine haut dosage. Resultats de l'etude SPESUB (suivi pharmaco-epidemiologique du Subutex en medecine de ville). Revue d'Epidemiologie et de Sante Publique 48:363-373
Naef (1999)	Reduced infections with HIV and hepatitis A during a Swiss intravenous opiate maintenance program. Journal of Acquired Immune Deficiency Syndromes: JAIDS 21(4):349-351
Reimer (2011)	Physical and mental health in severe opioid-dependent patients within a randomized controlled maintenance treatment trial. Addiction 2011; 106(9):1647-1655
Sagliocca (1997)	A morphine prescription program in Italy (1980-1985): Retrospective evidence of protection against HIV/AIDS. Addiction Research 5(2):137-144
Sendi (2003)	Intravenous opiate maintenance in a cohort of injecting drug addicts. Drug and Alcohol Dependence 69 (2):183-188
Steffen (2001)	HIV and hepatitis virus infections among injecting drug users in a medically controlled heroin prescription programme. European Journal of Public Health 11 (4):425-430