European Monitoring Centre
for Drugs and Drug Addiction

TECHNICAL REPORT

Evidence for the effectiveness of interventions to prevent infections among people who inject drugs

Part 2:
Drug treatment for preventing hepatitis C,
HIV and injecting risk behaviour

ECDC AND EMCDDA TECHNICAL REPORT

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EUROPEAN CENTRE FOR
DISEASE PREVENTION
AND CONTROL

European Monitoring Centre
for Drugs and Drug Addiction

Contents

Acronyms and glossary

AOR	Adjusted odds ratio
BBV	Blood-borne virus
BMT	Buprenorphine maintenance therapy
CBT	Cognitive behavioural therapy
CI	Confidence interval
CM	Contingency management
ECDC	European Centre for Disease Prevention and Control
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IFN	Interferon
IOM	Institute of Medicine
IRR	Incidence rate ratio
MMT	Methadone maintenance therapy
NIDA	National Institute on Drug Abuse
NSP	Needle and syringe exchange programme
OR	Odds ratio
OST	Opioid substitution therapy
PWID	People who inject drugs
pIFN	Pegylated interferon
RBV	Ribavirin
RCT	Randomised controlled trial
RR	Relative risk
SVR	Sustained virological response
WHO	World Health Organization
UNDCP	United Nations Office on Drugs and Crime Prevention

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Executive summary

Introduction

The aim of the literature review presented in this report was to provide evidence to inform the recommendations made by ECDC and the EMCDDA in the 2011 'Guidance on the prevention and control of infectious diseases among people who inject drugs'.

The evidence presented here focuses on the effectiveness of drug treatment on the occurrence and risk of hepatitis C virus (HCV), hepatitis B virus (HBV) and human immunodeficiency virus (HIV); the progression of HIV; and/or injecting risk behaviour in people who inject drugs. Additional evidence on the effectiveness of drug treatment is covered in a companion technical report 'Evidence for the effectiveness of interventions to prevent infections among people who inject drugs, Part 1: Needle and syringe programmes and other interventions for preventing hepatitis C, HIV and injecting risk behaviour'. The evidence included here is based on research published in the literature: this report does not present exhaustive evidence for effectiveness of public health interventions, as different types of evidence may be considered, such as evidence based on expert opinion or stemming from 'best implementation practices'. There are also other reasons for providing some of the interventions reviewed here, such as to attract and attach users to services and, while such outcomes were out of the scope of this review, these factors may provide rationale to include certain interventions as part of successful multi-component intervention programmes, even in the absence of their effectiveness in decreasing hepatitis C, HIV, and injecting-risk behaviour.

Methods

Appraisal of literature in this chapter was carried out using a 'review of reviews' methodology developed by the Health Development Agency (Kelly et al., 2002), which aims to bring together evidence from published reviews rather than undertaking a systematic search of primary literature. The review of reviews methodology involved a systematic search of the literature for published reviews; identification of relevant systematic, meta-analytic and narrative reviews; critical appraisal of the reviews; and synthesis of the findings. This report focused on the appraisal and synthesis of evidence regarding the effectiveness of drug treatment on the occurrence and risk of HCV, HBV and HIV in people who inject drugs.

Main findings

Analysis of the evidence indicates that the majority of studies regarding the prevention of blood-borne viruses (BBVs) in people who inject drugs (PWID) relate to the impact of opioid substitution treatment (OST), with comparatively fewer studies available regarding other forms of treatment. However, there is strong evidence at the level of reviews to support the effectiveness of OST, in particular methadone maintenance therapy (MMT), in reducing HIV transmission and self-reported injecting risk behaviour. There is also moderate evidence which indicates that OST is effective in reducing HCV transmission. Evidence indicates that OST reduces injecting risk behaviour among PWID in prison, but there is insufficient evidence in the prison setting to draw conclusions regarding the impact of OST in reducing HIV or HCV transmission.

There is currently not enough evidence at the level of reviews to draw conclusions regarding the impact of other forms of drug treatment on HIV or HCV transmission or injecting risk behaviour, but moderate review-level evidence supports the use of psychosocial approaches alongside OST in relation to opioid use, compliance, and completion of treatment. There is a relative lack of sufficient evidence regarding effective drug treatment approaches to reduce the transmission of HIV or HCV among people who inject stimulants and other non-opioid substances. A growing body of evidence demonstrates that the combination of OST and needle and syringe programmes (NSP) is more effective in reducing HIV or HCV incidence and injecting risk behaviour than either approach alone.

In HIV-positive PWID, OST increases adherence to antiretroviral therapy (ART) and, thereby, the likelihood of achieving virological success. However, there is currently not enough review-level evidence to draw conclusions regarding the effectiveness of OST in increasing compliance and/or virological success in response to HCV treatment.

Overall, evidence supports the role of pharmacological opioid substitution treatment in reducing transmission and progression of HIV, and a reduction in the risk of HCV seroconversion, when provided at adequate doses over a sufficient time period.

1 Background and aim

In 2011, the European Centre for Disease Prevention and Control (ECDC) and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) sought to review the scientific evidence base for the ECDC–EMCDDA Guidance on the prevention of infectious disease among people who inject drugs. The aim of this report was to provide an up-to-date body of scientific evidence to enable decision-making on topics to be included in the guidance by:

- synthesising the available review-level research evidence as well as more recent primary research on the effectiveness of drug dependence treatment in reducing the transmission of HCV, HIV and injecting risk behaviour.

Drug treatment plays a critical role in addressing BBV-associated harm in PWID. Drug treatment reduces the risk of transmitting or contracting HIV, HCV or HBV through contaminated equipment by terminating or reducing drug use, reducing the frequency of injecting; or altering injecting risk behaviour (Palmateer, 2008; Tilson et al., 2007). The benefits of drug treatment extend to reductions in opioid-induced overdose; drug-related crime; and physical and psychological wellbeing (World Health Organization, 2004), but this report will focus only on the impact of drug treatment on BBV-associated harm.

Drug treatment encompasses a range of strategies to manage injecting drug use, including pharmacological maintenance treatment or opioid substitution treatment (OST); pharmacological detoxification treatment; pharmacotherapy combined with psychosocial approaches such as counselling or contingency management; and residential rehabilitation (Amato et al., 2008a; Kimber, 2010; WHO, 2009). Of these strategies, evidence regarding the effectiveness of drug treatment in preventing BBV-associated harm is strongest in relation to the impact of OST in opiate-dependent PWID. At present, there are comparatively fewer studies regarding the effectiveness of drug treatment for stimulant or cocaine-dependent PWID, although evidence suggests that this is a growing problem in some parts of Europe (EMCDDA).

Pharmacotherapy for opioid dependence involves the use of agonist and antagonist agents. Opioid agonist treatments, such as methadone and the partial agonist buprenorphine, can be used either for detoxification or longer-term maintenance treatment. Methadone maintenance treatment (MMT) and buprenorphine maintenance treatment (BMT) are the most commonly prescribed forms of OST, and these treatments prevent withdrawal symptoms, reduce cravings associated with opiate use, and reduce the effects of illicit opiates. Such therapy is most effective when it is continuous and is provided at adequate doses of over 60 milligrams (mg) per day (Amato et al., 2005; Faggiano et al., 2003a). Treatment with opioid antagonists, such as naltrexone, can help to reduce relapse to opioid use following opioid withdrawal by blocking the effects of heroin or other opioids (Tilson, Aramrattana, Bozzette, et al., 2007; WHO, 2009). Current guidelines from the World Health Organization (WHO) recommend that opioid agonist maintenance treatment such as MMT be provided for opioid-dependent individuals in the first instance (WHO, 2009).

OST can be provided in conjunction with psychosocial treatments such as individual counselling, family or couple therapy; cognitive behavioural therapy; motivational interviewing; or contingency management, which involves the provision of rewards for individuals that remain abstinent from drugs or who meet specific objectives of treatment. Evidence indicates that the combination of these approaches offers benefit in terms of retention of PWID in treatment, compliance with treatment and lower drug use (Amato et al., 2008b).

In 2010, it was estimated that approximately 670 000 people were receiving OST in Europe, with the total number of OST clients representing approximately 50% of the number of problematic opiate users in the European Union. However, data demonstrate that national variations in coverage are evident, varying from below 10% to over 50% of opioid users receiving OST in countries for which such data are available (EMCDDA, 2010a; EMCDDA, 2010b). Such coverage is important, since studies have indicated that countries with the greatest provision of NSP and OST between 2000 and 2004 had lower incidence of HIV in subsequent years (Wiessing et al., 2009).

This report reviews evidence regarding the effectiveness of drug treatment, in particular OST, in relation to the prevention of transmission of blood-borne viruses HIV and HCV, and the reduction of injecting risk behaviours and injection frequency. The report also briefly describes evidence relating to the impact of OST on adherence to, and virological success of, antiretroviral therapy (ART) in HIV-positive PWID; and the impact of HCV treatment in HCV-positive PWID. We focus on evidence synthesised in recent reviews, supplemented where necessary with recently published primary literature, i.e. individual research studies.

2 Methods

In the UK in 2008, in the context of a significant number of people infected with HCV, a collaboration was established to review and summarise the available research evidence on the effectiveness of harm reduction interventions in the prevention of HCV among PWID. As time and resources did not permit a full systematic review of the range of potential interventions, a 'Review of Reviews' (RoR) approach was used. The RoR method is a method of systematically bringing together the evidence captured in reviews which themselves have captured evidence from primary studies. Results of this original RoR exercise have been published previously in peer-reviewed journals and grey literature reports (Kimber et al., 2010; Palmateer et al., 2010; Palmateer et al., 2008). The present report updates the original RoR.

Appraisal of literature in this chapter was carried out using a 'review of reviews' methodology developed by the Health Development Agency (Kelly et al., 2002), which aims to bring together evidence from published reviews rather than undertaking a systematic search of primary literature. The review of reviews methodology involved a systematic search of the literature for published reviews; identification of relevant systematic, meta-analytic and narrative reviews; critical appraisal of the reviews; and synthesis of the findings. This report focused on the appraisal and synthesis of evidence regarding the effectiveness of drug treatment on the occurrence and risk of HCV, HBV and HIV in people who inject drugs. Gaps and inconsistencies in the evidence base were identified where relevant to highlight areas that require further research.

Relevant reviews were identified by searching the electronic databases CINAHL, the Cochrane Library, Embase, MEDLINE and PsycINFO using the OvidSP platform. Publications of key international agencies for harm reduction grey literature were also searched, including: the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), the National Institute on Drug Abuse (NIDA), the US Institute of Medicine (IOM), the United Nations Office on Drugs and Crime Prevention (UNDCP), and the World Health Organization (WHO). Search strategies included a mixture of medical subject headings (MESH terms) and textual words to maximise the retrieval rate. Search terms are listed in Appendix 1.
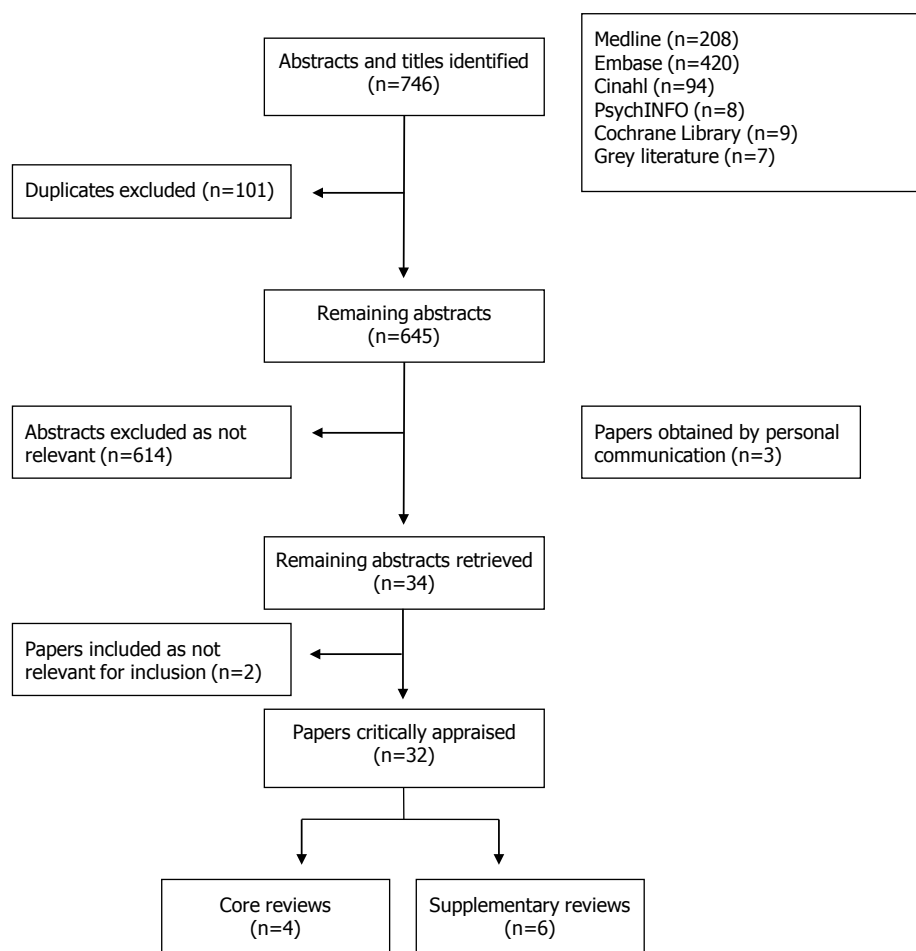
The criteria for inclusion of studies were: publication in English language; systematic reviews, syntheses and meta-analyses; publication date between 2000 and 2010; and consideration of the effectiveness of drug treatment in relation to HCV, HBV or HIV incidence/prevalence, progression of HIV, and/or injecting risk behaviour. Reviews published before 2000 were not included because reviews published in the 1980s and 1990s had been superseded by more recent publications. Studies regarding the cost-effectiveness of drug treatment, the effect of drug treatment on incidence/prevalence of bacterial infection, the impact of drug treatment on overdose mortality, and the impact of drug treatment on sexual transmission of BBVs were excluded from analysis for this report.

Literature searches for primary studies regarding the impact of drug treatment in relation to HIV or HCV incidence or injecting risk behaviour and published between 2009 and 2010 were also carried out, in case these had been excluded from recently published reviews. The same search terms were used in these searches, excluding those terms relating to the identification of review-level evidence. Primary literature searches were not carried out to obtain evidence regarding the impact of OST on outcomes of anti-retroviral treatment.

The content of this chapter updates previous publications on this topic, including a review of reviews of harm reduction interventions (Palmateer et al., 2008; Palmateer et al., 2010) and an updated summary of evidence published in EMCDDA monograph 10 (Kimber et al., 2009). These documents were used as the basis for discussion around the effectiveness of opioid substitution treatment in relation to HIV or HCV incidence and injecting risk behaviour. Sections of this chapter relating to the effectiveness of OST combined with psychosocial treatment, and the effectiveness of OST in relation to adherence to and/or effectiveness of anti-(retro)viral therapy, were not covered in the above publications (Palmateer et al., 2008; Kimber et al., 2009).

Literature was evaluated by two reviewers to determine whether the paper met the criteria for inclusion in the guidance. Selected reviews were critically appraised using a tool that considers the rigour of the methods used to identify the relevant literature (e.g. databases searched, specification of search terms, inclusion and exclusion criteria), the extent and rigour of the appraisal of the primary literature, the quality of the analysis in the case of meta-analysis, and the appropriateness of the conclusions (Kelly et al., 2002; Kimber et al., 2009; Palmateer et al., 2010) (see Appendix 2 for the appraisal tool). A depiction of the selection process and the number of papers excluded at different stages can be found in Figure 1.

Figure 1. Publications identified for the review of reviews

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                              ┌─────────────────────────┐         ┌────────────────────────────┐
                              │ Abstracts and titles     │         │ Medline (n=208)            │
                              │ identified               │         │ Embase (n=420)             │
                              │ (n=746)                  │         │ Cinahl (n=94)              │
                              └─────────────────────────┘         │ PsychINFO (n=8)            │
                                         │                         │ Cochrane Library (n=9)     │
    ┌─────────────────────────┐          │                         │ Grey literature (n=7)      │
    │ Duplicates excluded      │◄─────────┤                         └────────────────────────────┘
    │ (n=101)                  │          │
    └─────────────────────────┘          ▼
                              ┌─────────────────────────┐
                              │ Remaining abstracts      │
                              │ (n=645)                  │
                              └─────────────────────────┘
                                         │
    ┌─────────────────────────┐          │                         ┌────────────────────────────┐
    │ Abstracts excluded as not│◄─────────┤                         │ Papers obtained by personal│
    │ relevant (n=614)         │          │                         │ communication (n=3)        │
    └─────────────────────────┘          ▼                         └────────────────────────────┘
                              ┌─────────────────────────┐
                              │ Remaining abstracts      │
                              │ retrieved (n=34)         │
                              └─────────────────────────┘
                                         │
    ┌─────────────────────────┐          │
    │ Papers included as not   │◄─────────┤
    │ relevant for inclusion   │          │
    │ (n=2)                    │          ▼
    └─────────────────────────┘ ┌─────────────────────────┐
                              │ Papers critically         │
                              │ appraised (n=32)          │
                              └─────────────────────────┘
                                    │             │
                                    ▼             ▼
                        ┌──────────────┐  ┌──────────────────┐
                        │ Core reviews │  │ Supplementary    │
                        │ (n=4)        │  │ reviews (n=6)    │
                        └──────────────┘  └──────────────────┘
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The highest quality reviews for which the whole review or part of the review were judged to be of sufficient quality based on meeting sufficient criteria in the above tool (Kelly et al., 2002) were considered to be 'core' reviews, which formed the basis from which to derive evidence statements about the effectiveness of harm reduction interventions. Those reviews considered of insufficient quality to rely on the author's conclusions using the critical appraisal tool, but viewed as providing complementary information on the effectiveness of the interventions, were retained as 'supplementary' reviews. This method of classification of review-level evidence has been utilised in related studies published elsewhere (Kimber et al., 2009; Palmateer et al., 2010).

From each review, information was extracted on the reviewers' assessment of the evidence and the number, design and findings of the relevant primary studies included in the review. The level of review evidence that supported or discounted the effect of an intervention was classified as: (i) sufficient, (ii) tentative; (iii) insufficient; or (iv) no evidence from reviews. The classifications are based on a framework that considers the quality of the reviews, the reviewers' conclusions and the designs/findings of the primary studies as depicted in Table 1 below (Ellis et al., 2003).

Table 1. Types of evidence statements and the level of evidence that was required to support each statement

Sufficient review-level evidence	Level of evidence
Sufficient review-level evidence	Clear and consistent statements from one or more core review papers based on multiple robust studies, *or*
	consistent evidence across multiple robust studies within one or more core reviews, where no clear statement of the evidence is given in the review(s).
Tentative review-level evidence	A tentative statement of evidence from one or more core reviews based on consistent evidence from a small number of robust studies or multiple weaker studies, *or*
	consistent evidence from a small number of robust studies or multiple weaker studies within one or more core reviews, where no clear statement of the evidence is given, *or*
	conflicting evidence from one or more core reviews, with the stronger evidence weighted towards one side (either supporting or discounting effectiveness) and a plausible reason for the conflict, *or*
	consistent evidence from multiple robust studies within one or more supplementary reviews.
Insufficient review-level evidence	A statement of insufficient evidence from a core review.
	Some evidence, but insufficient to either support or discount the effectiveness of an intervention (either because there is too little evidence or the evidence is too weak), in the absence of a statement of evidence from a core review.
	Anything less than consistent evidence from multiple robust studies within one or more supplementary reviews.
No review-level evidence	No core or supplementary reviews of the topic identified, possibly due to a lack of primary studies.

Modified from Ellis et al., 2003

Consistent with an evidence-based medicine approach (Glaziou and Heneghan, 2009; Sackett et al., 1996), study designs considered to provide more robust evidence of effect were randomised controlled trials (RCTs), longitudinal cohort studies, and case-control designs, while ecological, serial cross-sectional and cross-sectional designs were considered to provide 'weaker' evidence of effect. Although there may be distinct approaches to rating the quality of evidence (Balshem et al., 2011; Guyatt et al., 2011), the primary aim of this chapter was to assess the quality of review-level evidence. Given the increasing number of reviews of the effectiveness of public health interventions in the literature, the aim of this approach is to enable the collation of reviews from such reviews, rather than to undertake a systematic review of the primary literature itself. Nevertheless, the importance of different study designs and data sources was not discounted in evaluating the process and impact of interventions.

No or weak evidence of effectiveness may primarily reflect the quality and/or number of studies available and does not necessarily indicate a lack of intervention effectiveness. We also acknowledge that the history of harm reduction interventions has to a large extent (and necessarily) been driven by community actions and pragmatic public health policies, with some interventions implemented in the absence of high-quality trials or intervention-based research.

Results of the review of reviews literature search are presented in Figure 1 above and Appendix Tables A3.1 and A3.2. Four core reviews and six supplementary reviews were identified relating to the effectiveness of drug treatment on the incidence/prevalence of HCV, HBV, or HIV; treatment of HIV or HCV; or injecting risk behaviour (See Appendix Tables A3.1 and A3.2).

3 Results

The evidence discussed in this chapter was identified and selected according to methodology described in the previous section, whilst results of the literature search are presented in Annex 3. Four core reviews and six supplementary reviews were identified relating to the effectiveness of drug treatment on the incidence/prevalence of HCV, HBV, or HIV; adherence to and/or success of anti(retro)viral treatment; or injecting risk behaviour. These reviews will provide the basis of the content described in this chapter.

3.1 Drug treatment for opiate-dependent people who inject drugs

3.1.1 Opioid substitution treatment

The majority of evidence regarding effectiveness of drug treatment in preventing the occurrence and risk of HIV and HCV relates to OST. A large body of evidence examines the impact of OST in relation to the reduction of HIV and HCV incidence as well as the reduction of injecting risk behaviour, and findings relating to these outcomes are discussed in turn below.

Impact on HIV incidence

Three core reviews identified studies addressing the impact of OST in relation to HIV incidence (Gowing et al., 2008b; Sorensen and Copeland, 2000a; Tilson, Aramrattana, Bozzette, et al., 2007). The three core reviews considered eight studies between them, including two randomised controlled trials (RCTs) (Dolan et al., 2003; Rhoades et al., 1998a), four cohort studies (Hartel and Schoenbaum 1998a; Metzger et al., 1993; Moss et al., 1994a; Williams et al., 1992b); one case-control study (Serpelloni et al., 1994) and one cross-sectional study (Novick et al., 1990).

Three cohort studies showed the odds of HIV seroconversion were greater for untreated individuals or those with interrupted MMT compared to those who remained continuously in MMT (Metzger et al., 1993; Moss et al., 1994b; Williams et al., 1992a), whilst a cohort study and case-control study showed that lower daily dose and more time out of MMT was also associated with higher risk of HIV seroconversion (Hartel and Schoenbaum 1998b; Serpelloni et al., 1994). In an RCT of 50 mg versus 80 mg MMT, no seroconversions occurred in six months of follow-up (Rhoades et al., 1998a). A retrospective cohort study found no HIV seroconversions among long-term MMT patients (Novick et al., 1990) and an RCT of MMT in prison found no difference in HIV incidence between those in MMT and waitlist controls, although this was in the context of a short period of follow-up and low HIV prevalence (Dolan et al., 2003).

The conclusions from all three reviews highlighted that continuous MMT is associated with lower rates of HIV seroconversion. However, it was acknowledged that those who resist treatment or engage in risky behaviours may leave treatment, while those with fewer HIV risk behaviours may stay in treatment longer. In addition, none of the reviews included a meta-analysis, partly owing to concerns over heterogeneity and differences in the ways that studies were conducted and reported, so there is currently no summary measure of OST treatment effect.

Specifically, Gowing et al. (2008) concluded that:

'Few data and variability in the means of reporting limit the conclusiveness of any analysis, but these studies consistently indicate lower rates of [HIV] seroconversion associated with substitution treatment. This suggests that reductions in risk behaviour do translate into actual reduction in cases of HIV infection.' (p. 22).

Tilson et al. (2007) also concluded that:

'Modest evidence from prospective cohort and case-control studies shows that continuous opioid agonist maintenance treatment is associated with protection against HIV seroconversion. This association persists after controlling for many confounders. These studies also show that the risk of HIV seroconversion is inversely related to length of time in treatment. However, the possibility of bias in these findings from self-selection cannot be ruled out.' (p. 92)

Sorensen and Copeland (2000) concluded that:

'Four out of the six studies reviewed... provided firm evidence for the protective effect of MMT against HIV seroconversion. These findings are more convincing because they are based on biologically verified outcomes rather than participants self-report...[but] nearly all the studies are inherently limited by a self-selected treatment sample... in most of the studies the in-treatment and out-of-treatment groups differ on demographics and that

there may be other unidentified differences in these groups that may account for the differences found in HIV seroconversion.' (p. 27)

In addition to evidence identified in the above reviews, a primary literature search identified an additional RCT carried out in drug treatment centres in Bangkok, Thailand, as part of a HIV vaccine trial (Suntharasamai et al., 2009). The study reported that participation in MMT during the previous six months was associated with a statistically significant reduction in risk of HIV infection (adjusted hazard ratio 0.6 (95% confidence interval [CI] 0.4–0.8)). The vaccine did not prevent HIV infection so this effect was independent of receipt of the vaccine.

Studies also indicate that combination approaches involving OST and NSP may be effective in reducing HIV incidence. First, a European study (Van Den Berg et al., 2007a) suggested that full participation in combined harm reduction interventions, NSP and OST, reduced HIV incidence by 57% (incidence rate ratio [IRR] 0.43, 95% CI 0.21–0.87), whereas participation in OST or NSP alone did not lead to a significant reduction in HIV incidence.

Furthermore, one primary study carried out at a drug detoxification programme in New York City (Des Jarlais et al., 2010) compared the effectiveness of a 'combined prevention program' (methadone maintenance, education and outreach, risk reduction, HIV testing and needle exchange) with an 'initial prevention program' excluding needle exchange (methadone maintenance, education and outreach, risk reduction, HIV testing) in relation to HIV transmission. Data regarding PWID in the initial prevention program were collected over a four year period (1990–1994) for individuals who began injecting between 1984 and 1994, whilst data regarding those in the combined prevention programme were collected over a period of thirteen years (1995–2008) for individuals who began injecting in 1995. The authors reported that the prevalence of HIV increased over time to a greater extent in those on the limited programme compared to those on the combined programme (21% compared to 6%; OR CPE to IPE 0.23, 95% CI 0.15–0.34), suggesting that OST combined with other prevention strategies was effective in limiting HIV transmission.

Summary of evidence

Evidence in three core reviews demonstrates that there is sufficient review-level evidence to conclude that OST in community settings is effective in reducing HIV seroconversion, especially for those in continuous treatment.

Primary evidence also suggests that the combination of OST and NSP may be effective in reducing HIV incidence.

Impact on HCV incidence

Review-level evidence regarding the effectiveness of OST with respect to HCV seroconversion is less clear compared to evidence regarding HIV seroconversion. However, one supplementary review considered evidence of the effect of OST on HCV seroconversion (Wright and Tompkins 2006) and a recent meta-analysis of UK-based studies, alongside additional primary studies, provide support for the effectiveness of OST in reducing HCV incidence (Craine et al., 2009; Hallinan et al., 2007; Van Den Berg et al., 2007b; Turner et al., 2011)).

Wright and Tompkins (2006) identified six cohort studies and a case-control study. A cohort and a case-control study found a non-significant trend toward lower HCV incidence among those in MMT compared to those not in treatment (Rezza et al., 1996) or those who have left treatment (Thiede et al., 2000). However, a Dutch cohort study found MMT (in combination with NSP) was not associated with any decreases in annual HCV incidence over four years (Van Ameijden et al., 1993) and a more recent paper from the Amsterdam Cohort Study (Van Den Berg, et al., 2007a) identified in a primary literature search reported that MMT alone over a six-month period was not associated with lower risk of HCV seroconversion. Three cohort studies did not find any differences in HCV incidence between those in MMT and those not in MMT (Chamot et al., 1992; Crofts et al., 1997; Selvey et al., 1997) and one cohort study found no difference in risk of HCV seroconversion among PWID recruited from MMT clinics and PWID recruited from NSPs (Maher et al., 2006).

Based on the available evidence, Wright and Tompkins concluded that:

'As regards methadone maintenance therapy, whilst it has been successful in reducing the incidence of HIV, the evidence for its effectiveness in reducing HCV incidence is less convincing.' (p.5)

However, a primary literature search identified four additional community-based studies of HCV and OST, three of which were cohort studies that suggested a positive impact of OST. HCV incidence was lower among those in continuous OST compared to those with interrupted OST (Hallinan et al., 2005); MMT in the past six months was protective against both primary infection in non-infected PWID and secondary HIV and HCV infection (i.e. infection with HIV or HCV in mono-infected PWID) (Miller et al., 2004); and HCV incidence was similar among those who were not in OST during follow-up or in OST for up to six months, but was lower amongst those in treatment for seven to 12 months (Craine et al., 2009). In the Amsterdam Cohort Study described above (Van Den Berg et al., 2007a), full participation in both MMT and NSPs over a six-month period was associated with a lower risk of HCV infection, albeit that MMT alone was not associated with such an effect. In support of the latter finding, the UK-

based cohort study mentioned above (Craine et al., 2009) also noted a greater impact of OST on reducing HCV incidence when combined with NSP.

Most recently, and in support of the findings of van den Berg et al. (2007), a meta-analysis of the effectiveness of the use of OST and NSP in relation to HCV incidence in the UK identified that OST and NSP independently reduced HCV incidence in PWID. OST was associated with a 55% reduction in the risk of new HCV infection (adjusted OR [AOR] OST 0.45, 95% CI 0.25–0.82; see Figure 2) (Turner et al., 2011). In addition, OST and NSP acted synergistically such that PWID with full participation in harm reduction were at lowest risk of HCV seroconversion compared to those on minimal harm reduction (AOR 0.21, 95% CI 0.08–0.52). The meta-analysis included six UK-based studies that collected individual-level data on intervention coverage as well as a measure of newly-acquired HCV infection amongst PWID in the community. The sample sizes of individual studies included in the meta-analysis varied between 299 and 947 participants.

The meta-analysis provides strong evidence for the effectiveness of OST in reducing HCV incidence in the UK (see Figure 2 below) since it gives a summary estimate of the impact of OST. The combination of data from primary studies by meta-analysis is particularly important since primary research studies that have weak methodology or insufficient power to detect an effect may be deemed insufficient for inclusion in reviews and might therefore be excluded from evidence syntheses of this kind.

Figure 2. **Meta-analysis of the effect of opioid substitution treatment on HCV incidence**

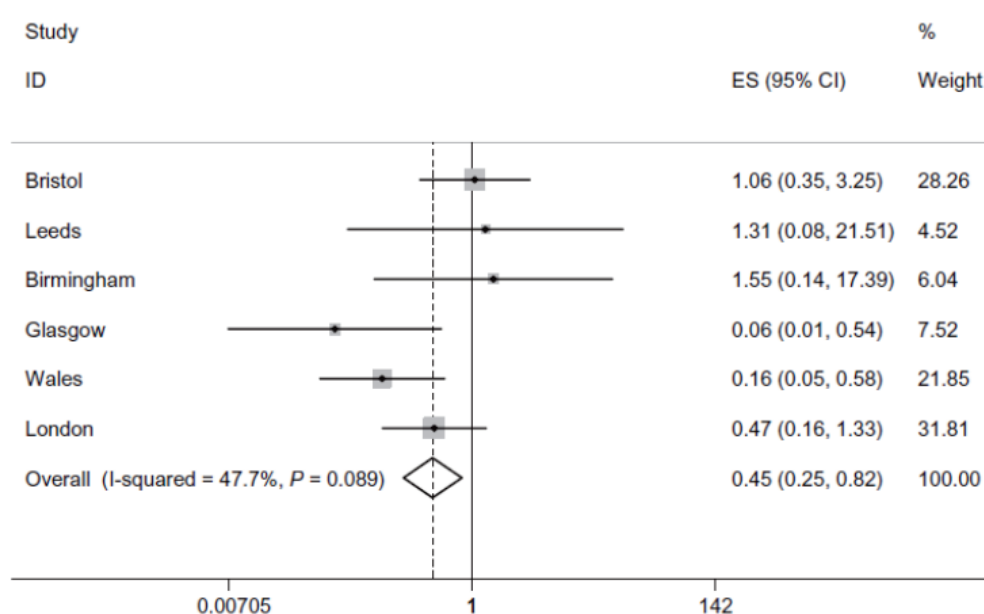| Study ID		ES (95% CI)	% Weight
Bristol		1.06 (0.35, 3.25)	28.26
Leeds		1.31 (0.08, 21.51)	4.52
Birmingham		1.55 (0.14, 17.39)	6.04
Glasgow		0.06 (0.01, 0.54)	7.52
Wales		0.16 (0.05, 0.58)	21.85
London		0.47 (0.16, 1.33)	31.81
Overall (I-squared = 47.7%, P = 0.089)		0.45 (0.25, 0.82)	100.00

Figure reproduced from Turner et al., 2011.

Summary of evidence

Consistent evidence from multiple longitudinal studies within supplementary reviews shows a weak or absent association between OST and a reduction in HCV incidence. However, a recent meta-analysis of UK studies, taken together with primary studies, provides tentative evidence of the effectiveness of OST in reducing HCV incidence. A meta-analysis of all relevant studies is required to provide sufficient evidence of benefit.

Impact on injecting risk behaviour

A large body of evidence has examined the impact of OST on injecting risk behaviour in PWID, and studies included in three core reviews have demonstrated beneficial impacts of OST in relation to injecting risk-related outcomes. Three core reviews assessed the effect of OST on injecting risk behaviour (Gowing et al., 2008a; Sorensen and Copeland 2000b; Tilson et al., 2007). Since the measurement of injecting risk behaviour was heterogeneous, evidence was categorised into three domains: prevalence and frequency of injection; sharing of injecting equipment; and scores of drug-related risk, and findings are discussed for each outcome in turn. A summary of the text can be found in Table 1 on page 13 below.

Injection frequency
Gowing et al. (2008) identified one RCT (Dolan et al., 2003) and six cohort studies that reported the prevalence of injecting drug use before and after OST (Camacho et al., 1996; Chatham et al., 1999; Gossop et al., 2000; King et al., 2000; Magura et al., 1991; Teesson et al., 2006); three RCTs (Dolan et al., 2003; Lott et al., 2006; Strang et al., 2000) and six cohort studies that reported frequency of injection at baseline and follow-up (Brooner et al.,

1998; Camacho, et al., 1996; Chatham et al., 1999; Kwiatkowski and Booth, 2001; Simpson et al., 1995) and two cohort studies that examined both the proportion and frequency of injection (Camacho et al., 1996; Chatham et al., 1999). Tilson et al. (2007) identified the same studies with the exception of Teesson et al. (2006) and Lott et al. (2006).

All studies showed statistically significant reductions in injecting risk behaviour from baseline to follow-up despite being varied in terms of follow-up periods (range three to 12 months) and the measurement of frequency of injecting (Gowing et al., 2008a; Tilson et al., 2007).

Sorensen and Copeland (2000) included a further nine studies with data on injection prevalence and frequency: one RCT and four cohort studies of in-treatment samples showed retention in MMT was associated with decreases in injection frequency (Abbott et al., 1998a; Ball et al., 1988; Iguchi 1998; Saxon et al., 1994a; Shore et al., 1996); and one cohort and three cross-sectional studies comparing those in treatment with non-treatment samples found that MMT was associated with fewer injections (Baker et al., 1995; Greenfield et al., 1995; Meandzija et al., 1994; Stark et al., 1996a).

One supplementary review (Degenhardt et al., 2010) identified an additional cohort study (Wong et al., 2003) which examined the impact of MMT in PWID over an eight-week period in Hong Kong and found that clients that attended the methadone clinic more than twice in the last week had lower levels of injecting drug use in the past 30 days.

A primary literature search also identified one RCT (Wilson et al., 2010) and four prospective cohort studies (Choopanya et al., 2003; Corsi et al., 2009; Gossop et al., 2003; Kimber et al., 2010).

The RCT (Wilson et al., 2010) examined the difference in HIV risk behaviours between those receiving interim methadone (IM) maintenance treatment and those assigned to a waiting list. Mean injection risk scores were lower in the IM group (19.7 compared to 37.2) and those receiving methadone were less likely to inject drugs compared to those in the control group (χ^2 5.20, p<0.03).

Among the cohort studies, Gossop et al. (2003) reported findings of a UK-based study showing that residential, community, and methadone maintenance treatment programmes reduced both injecting drug use and needle sharing; and receipt of methadone maintenance treatment was associated with reductions in injecting risk behaviour in a cohort of PWID in Bangkok, Thailand (Choopanya et al., 2003). A US-based prospective cohort study (Corsi et al., 2009) assessed the impact of MMT on HIV risk behaviour and drug use over a six-month period, reporting a non-significant reduction in injection frequency amongst participants receiving MMT for longer time periods. Lastly, a UK-based prospective cohort study (Kimber et al., 2010) reported that OST was associated with an increased time period to long-term cessation of injecting. Among those that achieved long-term cessation of injecting, those not exposed to OST had a lower total number of days injecting compared to those that were exposed to OST (878 vs. 1469 days; t=-0.9; p=0.36). Nevertheless, those exposed to OST reported significantly lower frequency of injecting during periods of treatment compared to periods without OST (mean 157 vs. 273 days per year; t=-3.9; p<0.001).

Sharing of equipment
Gowing et al. (2008) identified three RCTs and six cohort studies that examined the proportion who reported sharing equipment before and after a period of MMT. Tilson et al. (2007) identified the same studies except for Teesson et al. (2006) and Schroeder et al. (2006).

Eight of nine studies found a significant reduction in sharing between baseline and follow-up (Camacho et al., 1996; Chatham et al., 1999; Dolan et al., 2003; Margolin et al., 2003; Schroeder et al., 2006; Teesson et al., 2006) (Gossop, et al., 2000; Grella et al., 1996), whilst the ninth study found a non-significant reduction in reported sharing (King et al., 2000).

Sorensen and Copeland (2000) additionally included one RCT and three cohort studies of in-treatment samples that showed that retention in MMT was associated with decreased sharing of injecting equipment (Camacho et al., 1996; Magura et al., 1998; Rhoades et al., 1998b; Saxon et al., 1994b) whilst one cross-sectional study found no differences in sharing between new treatment entrants and the rest of the sample (Calsyn et al., 1991). One cohort study and four cross-sectional studies comparing those in treatment with non-treatment found MMT was associated with decreased sharing (Caplehorn and Ross 1995; Greenfield et al., 1995; Klee et al., 1991; Longshore et al., 1993; Stark et al., 1996b) and one cross-sectional study found no differences in sharing (Baker et al., 1995).

One supplementary review (Degenhardt et al., 2010) identified an additional study that demonstrated a significant association between methadone treatment (detoxification with or without maintenance or MMT only) and decreased frequency of needle sharing at baseline among PWID participating in a vaccine trial in Bangkok. The study also demonstrated that the proportion of participants reporting needle sharing was lower among those receiving MMT at 6 months and 12 months (van Griensven et al., 2004).

A primary literature search identified the cohort study described above (Corsi et al., 2009). The study demonstrated that a greater number of days receiving MMT was significantly associated with reduced sharing of

paraphernalia at follow-up. Wilson et al. (2010) reported that those receiving IM had lower likelihood of injecting drugs with others and a lower likelihood of using the same cooker, cotton or rinse water.

HIV risk scores

Gowing et al. (2008) identified four RCTs, one cohort and two cross-sectional studies comparing drug-related HIV risk scores among those in and out of OST (Abbott 1998b; Avants et al., 1998; Baker et al., 1995; Chatham et al., 1999; Mark et al., 2006; Marsch et al., 2005a; Sees et al., 2000). Tilson et al. (2007) identified the same studies except for Mark et al. (2006) and Marsch et al. (2005).

Four studies found significant decreases in drug-related HIV risk behaviour scores before and after OST (Abbott et al., 1998c; Avants et al., 1998; Chatham et al., 1999; Marsch et al., 2005b). Baker et al. (1995) and Mark et al. (2006) compared the drug risk scores for those currently in OST and not in OST, and in both studies the mean score was significantly lower for the cohort receiving OST at the time of interview. However, Sees et al. (2000) found no significant difference in mean risk scores between intake and six-month follow-up between MMT and methadone detoxification groups.

In summary, the conclusions of all three core reviews allowed that OST was associated with reductions in self-reported prevalence and frequency of injection, sharing of injecting equipment and injecting risk behaviour risk scores.

Gowing et al. (2008) concluded:

'Substitution treatment is associated with a significant decrease in the proportion of participants reporting injecting drug use and in the frequency of injection... [and] a significant decrease in the sharing of injecting equipment ... studies that reported [injecting risk behaviour] scores also showed a significant reduction in risk associated with substitution treatment.' (p. 19–20)

Tilson et al. (2007) concluded:

'Moderate to strong evidence from one RCT and a number of observational studies show that patients receiving methadone maintenance treatment report reductions in several drug-related HIV risk behaviours, including frequency of injecting and sharing of injecting equipment. These patients also had lower summary scores of drug-related risk behaviour compared with pre-treatment levels.' (p. 89)

Sorensen and Copeland (2000) concluded:

'26 out of 28 studies showed positive results in reducing HIV risk behaviours ... In this review both longitudinal studies of in-treatment samples and studies comparing treatment patients with other samples found very strong evidence that drug abuse treatment decreases the risk of HIV infection by decreasing needle-use. The evidence is less strong, but is still substantial, that drug abuse treatment changes the needle use patterns of participants (e.g. less needle-sharing, more use of sterile needles).' (p. 27–8)

Summary of evidence

Consistent evidence from multiple robust studies in core reviews indicates that there is sufficient review-level evidence to support the effectiveness of OST in reducing the frequency of injection, the sharing of injecting equipment and injecting risk behaviour.

Table 1. **Summary of findings of studies regarding the impact of pharmacological drug treatment on HIV risk behaviour**

Risk behaviour	Reviews	Studies identified	Summary of findings
Injection frequency	Gowing et al. (2008) Tilson et al. (2007) Sorensen and Copeland (2000)	RCTs: 4 Cohort studies: 14	All studies showed statistically significant reductions in injecting risk behaviour between baseline and follow-up.
	Sorensen and Copeland (2000)	RCTs: 1 Cohort studies: 5 Cross sectional studies: 3	Retention in MMT was associated with decreases in injection frequency. MMT was associated with fewer injections.
	Degenhardt et al. (2010)	Cohort studies: 1	Attendance at MMT clinic associated with lower levels of injecting drug use.

Risk behaviour	Reviews	Studies identified	Summary of findings
	Primary literature	RCTs: 1 Cohort studies: 4	MMT associated with lower mean injection risk scores and reduction in injecting drug use. Exposure to OST associated with lower levels of injecting during periods of treatment but increased time period to long-term cessation of injecting drug use.
Sharing of injecting equipment	Gowing et al. (2008) Tilson et al. (2007) Sorensen and Copeland (2000)	RCTs: 3 Cohort studies: 6	Eight of nine studies reported significant reduction in sharing between baseline and follow-up. One study reported non-significant reduction in reported sharing.
	Sorensen and Copeland (2000)	RCTs: 1 Cohort studies: 4 Cross-sectional studies: 4	Retention in MMT or treatment with MMT associated with decreased sharing of injection equipment.
	Sorensen and Copeland (2000)	Cross-sectional studies: 2	No difference in sharing between new treatment entrants and rest of sample or those in MMT with those not in MMT.
	Degenhardt et al. (2010)	RCTs: 1	MMT associated with less frequent needle sharing among PWID participating in a vaccine trial.
	Primary literature	RCTs: 1 Cohort studies: 1	Lower likelihood of injecting drugs with others and sharing equipment for those receiving interim MMT compared to those on a waiting list. Increased duration of MMT associated with decreased sharing.
Scores of drug-related HIV risk	Gowing et al. (2008) Tilson et al. (2007)	RCTs: 4 Cohort studies: 1 Cross-sectional studies: 2	Six studies: Significant decreases in HIV risk behaviour scores before and after OST or for individuals receiving or not receiving OST. One study: No significant difference between intake and follow-up for individuals receiving MMT compared to MMT detoxification.

3.1.2 Opioid substitution treatment and needle and syringe exchange programmes

In a recent meta-analysis of UK-based studies regarding the effectiveness of OST and NSP on HCV incidence outlined above (Turner et al., 2011), it was reported that PWID that participated in full harm reduction programmes, i.e. OST and NSP (≥ 100% sterile needles per injection), had lower injecting risk behaviours. Amongst those in full harm reduction treatment, the risk of needle sharing was reduced by 48%% (AOR 0.52, 95% CI 0.32–0.83) and mean injection frequency was reduced by 20.8 injections per month (95% CI -27.3 to -14.4). A smaller reduction in injection frequency was evident among those on OST and injecting but not exposed to high NSP coverage. High coverage of NSP without OST was associated with a non-significant reduction in HCV risk (AOR 0.73, 95% CI 0.44–1.22). As outlined above, the study also demonstrated that the risk of new HCV infection was 79% lower among PWID that participated in full harm reduction programmes compared to those on minimal harm reduction (AOR 0.21, 95% CI 0.08–0.52) (Turner et al., 2011).

Similar findings of additional benefit of a combination treatment approach were reported in a cohort study mentioned above (van den Berg, 2007). The study demonstrated that there was no significant association between receipt of MMT alone, or participation in needle and syringe exchange programmes and HIV or HCV seroconversion. However, full participation in a harm reduction programme (i.e. ≥ 60mg/day methadone and no current injecting or ≥ 60mg/day methadone and current injecting but all needles exchanged) was associated with a significantly reduced risk of HIV or HCV infection in ever-PWID (IRR 0.43, 95% CI 0.21–0.87 and IRR 0.36, 95% CI 0.13–1.03 respectively).

As outlined above, a recent study based in New York City also reported reduced HIV prevalence amongst PWID receiving a combined prevention programme (methadone maintenance, education and outreach, risk reduction, HIV testing and needle exchange) compared to those receiving a prevention programme excluding needle exchange (i.e. maintenance, education and outreach, risk reduction, HIV testing) (see section 1, page 7).

Summary of evidence

Evidence from one meta-analysis and two cohort studies indicates that participation in full harm reduction programmes involving OST and high coverage of NSP are associated with reductions in HIV and HCV incidence and reduced injecting risk behaviour.

As described above, a large body of evidence has been published regarding the impact of OST in relation to HIV or HCV incidence and injecting risk behaviour. However, fewer studies have examined the effectiveness of other forms of drug treatment in relation to such outcomes, with many studies reporting impacts of such treatments on outcomes such as completion of treatment, compliance and/or abstinence from drug use at follow-up. Whilst such measures do not provide clear or accurate measures of HIV/HCV incidence or associated harm, they provide an indication of potential benefit, and the effectiveness of other forms of drug treatment are therefore discussed in relation to those outcomes below.

3.1.3 OST and psychosocial treatment

Impact on injecting risk behaviour

Few studies have examined the impact of OST combined with psychosocial treatment in relation to HIV and/or HCV incidence. However, a number of studies have investigated the effectiveness of this combined approach in relation to retention in treatment, drug dependence and injecting risk behaviour.

One core review (Tilson et al., 2007) identified several studies that assessed the effect of psychosocial interventions combined with OST on HIV risk behaviours. However, a meta-analysis of four studies that evaluated the efficacy of combining psychosocial interventions with pharmacological treatment in relation to risk of HIV infection reported inconclusive findings (Prendergast et al., 2001).

In addition, one RCT that compared a 12-session harm reduction group intervention for PWID in a methadone maintenance programme with standard care of two hours of counselling per month and one risk reduction session reported that drug-related risk behaviour did not differ between the two groups (Avants et al., 2004). One further RCT among PWID on a methadone maintenance programme found that a relapse prevention programme involving six individual 60- to 90-minute sessions was associated with reduced rates of needle-risk behaviour during relapse compared to those receiving a brief intervention involving one 60- to 90-minute motivational session and a self-help booklet. There was no evidence that the brief intervention provided greater benefit than did methadone treatment alone (Baker et al., 1993).

Tilson et al. (2007) concluded:

'Few studies have specifically examined the impact of adjunctive psychosocial interventions on HIV risk behaviour among patients on opioid agonist maintenance therapy. Weak evidence from several studies suggests that some psychosocial interventions for patients enrolled in such therapy can be effective in reducing sexual and drug-related HIV risk behaviour, but more research is needed.'

Analysis of recent primary studies supports the conclusions of Tilson et al. (2007), demonstrating that the benefits of counselling combined with pharmacological treatment in relation to reducing injecting risk behaviour are unclear (Meade et al., 2010; Schottenfeld et al., 2008; Sullivan et al., 2008).

One longitudinal study (Sullivan et al., 2008) that assessed the impact of psychosocial counselling alongside buprenorphine and naloxone maintenance treatment on HIV risk behaviour demonstrated that opioid-dependent individuals receiving office-based buprenorphine/naloxone treatment in combination with psychosocial counselling in a primary care clinic showed significant reductions in overall and drug-related AIDS/HIV risk inventory scores at 12 and 24 weeks of follow-up compared to baseline. In addition, a non-significant reduction in the sharing of needles was observed between baseline and 12 or 24 weeks of follow-up. However, the provision of standard or extended psychosocial counselling alongside buprenorphine/naloxone did not affect the study outcomes (Sullivan et al., 2008).

One RCT (Schottenfeld et al., 2008) reported that there was no significant difference in HIV risk behaviours (i.e. ARI scores) among heroin-dependent patients at an outpatient clinic in Malaysia that had completed a 14-day inpatient detoxification protocol and subsequently received maintenance treatment with buprenorphine, naltrexone, or placebo alongside counselling over a 24-week period. Those assigned to counselling plus buprenorphine showed greater time to first heroin use than those receiving naltrexone or placebo; whilst buprenorphine and naltrexone-treated patients had a greater number of consecutive days abstinent from heroin. However, reductions in the frequency of injecting drug use were not significantly different between groups at three and six months of follow-up.

Furthermore, among young opiate-dependent PWID one RCT (Meade et al., 2010) demonstrated that the receipt of counselling plus extended buprenorphine/naloxone therapy over a 12-week period did not lead to a significant

reduction in injection risk (i.e. using dirty needles; sharing injecting equipment or slitting drug solution) compared to those receiving counselling plus a 14-day detoxification protocol with buprenorphine/naloxone. However, those in the group receiving buprenorphine/naloxone and counselling reduced injecting drug use to a greater extent than those receiving detoxification and counselling.

Impact on drug dependence and/or treatment-related outcomes

Evidence identified by Tilson et al. (2007) reported that contingency management (CM) provided to opioid-dependent individuals receiving methadone and concurrently dependent on non-opioid drugs can be effective in reducing drug use over particular time periods (Piotrowski et al., 1999a; Schottenfeld et al., 2005). In addition, evidence identified in a supplementary review (Degenhardt et. al. 2010) highlighted that psychosocial approaches combined with pharmacological approaches are beneficial with respect to reducing opiate use and/or compliance or completion of treatment (Amato et al., 2008a; Stanton and Shadish, 1997).

First, one systematic review and meta-analysis compared the impact of combined pharmacological treatment (MMT or BMT) and psychosocial treatment (CM, psychotherapeutic counseling; community reinforcement or family therapy) to the impact of pharmacological treatment alone, with respect to completion of treatment and opioid detoxification (Amato et al., 2008a). Nine RCTs were included. Evidence indicated that the addition of any psychosocial treatment to any pharmacological detoxification treatment was beneficial with regard to completion of treatment (relative risk [RR] 1.68, 95% CI 1.11–2.55), opiate use (RR 0.82, 95% CI 0.71–0.93); abstinence at follow-up (RR 2.43, 95% CI 1.61–3.66) when compared to pharmacological treatment alone. However, comparison between any psychosocial intervention plus MMT and MMT alone showed significant benefit in relation to the number of subjects abstinent at follow up (RR 2.46, 95% CI 1.61–3.76) and compliance as clinic absences (RR 0.48, 95% CI 0.38–0.59) but not for completion of treatment or drug use.

An earlier meta-analysis also reported that family and couple therapy delivered as an adjunct to MMT was more effective compared to individual counselling, peer group therapy and family psycho-education with respect to reducing drug use (Stanton and Shadish 1997).

> ## Summary of evidence
>
> There is insufficient evidence regarding the effectiveness of psychosocial plus pharmacological treatment in relation to HIV or HCV incidence or injecting risk behaviour. There is tentative review-level evidence of a beneficial impact of any psychosocial treatment provided alongside any pharmacological treatment with respect to compliance, completion of treatment and abstinence at follow-up.

3.1.4 Antagonist pharmacological treatment

Antagonist pharmacological treatment involves the use of naltrexone, which block the effects of heroin or other opioids and can help to reduce relapse to opioid use following opioid withdrawal (Tilson et al., 2007; WHO, 2009). The most frequently used form of such therapy is naltrexone, which helps to prevent relapse to opioid use following detoxification, although treatment with naltrexone may be associated with high attrition rates (Minozzi et al., 2006; Tilson et al., 2007). Treatment with opioid antagonist medication is frequently used for PWID who may not accept or have access to agonist maintenance therapy.

At present, there is insufficient evidence to assess the impact of antagonist pharmacological treatment in relation to HIV and HCV incidence in PWID. However, a number of studies have investigated the impact of such drug treatment in relation to injecting risk behaviour and retention in treatment, compliance and/or drug use during treatment and these are discussed in further detail below.

Impact on injecting risk behaviour

Evidence regarding the effectiveness of naltrexone was included in one core review (Tilson et al., 2007) and a Cochrane review (Minozzi et al., 2006).

Tilson et al. (2006) identified one RCT carried out in Russia which examined the effectiveness of oral naltrexone with or without fluoxetine, alongside counselling and support from family members or significant others, for preventing relapse and reducing HIV risk in abstinent opioid-dependent individuals (Krupitsky et al., 2006). The study demonstrated that no significant difference was observed in Risk Assessment Battery (RAB) drug risk scores between groups. Those receiving naltrexone were less likely to relapse and were more likely to remain in treatment at six months of follow-up, compared to those receiving placebo. However, it is possible that self-selection bias affected the findings since only 40% of those that dropped out of treatment could be followed-up.

Taking evidence up to 2009 into account, guidance from the WHO (2009) highlights that whilst the pharmacological treatment of opioid dependence should primarily involve agonist maintenance treatment such as MMT and BMT, PWID not commencing such treatment should consider antagonist pharmacotherapy using naltrexone, following the completion of opioid withdrawal.

Impact on drug dependence and/or treatment-related outcomes

One meta-analysis identified by one supplementary review and one core review (Degenhardt et al., 2010; Tilson et al., 2007) examined the effect of naltrexone versus placebo or other forms of drug treatment in reducing relapse in opioid-dependent persons following detoxification (Minozzi et al., 2006). The review, which included ten RCTs, indicated that naltrexone maintenance therapy either alone or in combination with psychosocial therapy is more efficacious than placebo alone or placebo in combination with psychosocial therapy in relation to reducing heroin use during treatment (RR 0.72, 95% CI 0.58–0.90). However, the effect was non-significant when comparisons between naltrexone treatment and placebo only were considered (RR 0.79, 95% CI 0.59–1.06). Critically, there was no evidence of a difference between groups with respect to relapse at follow-up or retention in treatment (Minozzi et al., 2006).

A systematic review (Lobmaier et al., 2008) identified by Degenhardt et al. (2010) identified one study that reported that higher doses of naltrexone (384 mg) are associated with a significant increase in the period of time in treatment compared to lower dose (192 mg) or placebo (Comer et al., 2006). However, Lobmaier et al. (2008) reported that there was insufficient evidence to evaluate the effectiveness of sustained-release naltrexone for the treatment of opioid dependence.

Tilson et al. (2007) identified an additional meta-analysis of 15 RCTs which compared naltrexone treatment with control. Only those subgroups with high retention showed lower drug use; and contingency management was associated with increased retention in treatment and use of naltrexone (Johansson et al., 2006).

> ### Summary of evidence
>
> There is insufficient review-level evidence regarding the effectiveness of naltrexone treatment in relation to HIV or HCV incidence or injecting risk behaviour. One meta-analysis reported a significant benefit of naltrexone alone or alongside psychosocial treatments compared to placebo in relation to a reduction in drug use. However, there is no evidence that naltrexone provides benefit with respect to relapse at follow-up or retention in treatment. Further research regarding the effectiveness of naltrexone in relation to HIV or HCV incidence and injecting risk behaviour is needed.

3.1.5 Psychosocial approaches

Impact on injecting risk behaviour

As outlined above, psychosocial interventions such as family therapy, psychosocial counselling and CM comprise a group of drug treatments that can be used alone or in combination with pharmacotherapy. Such approaches are particularly important for individuals that inject non-opioid substances. There is insufficient evidence to draw conclusions regarding the impact of psychosocial approaches alone in relation to HIV and HCV incidence. However, a number of studies have examined the impact on injecting risk behaviour. Studies in relation to the effectiveness of CM, cognitive behavioural therapy (CBT) and motivational interviewing were identified in one core review (Tilson et al., 2007) whilst a recent meta-analysis comparing psychosocial interventions with education of PWID was identified in one supplementary review (Degenhardt et al., 2010).

The meta-analysis identified by Degenhardt et al. (2010) compared multi-session psychosocial interventions for individuals or groups designed to reduce injecting risk behaviour with a standard education intervention consisting of one or two sessions only, or minimal intervention often involving provision of a self-help booklet. Multi-session psychosocial interventions did not provide benefit over standard education interventions with respect to injecting risk behaviour (RR 1.03, 95% CI 0.95–1.11) or minimal interventions. Furthermore, no difference was evident in relation to injecting risk behaviour in those receiving standard education interventions compared to minimal interventions (RR 1.10, 95% CI 0.92–1.31) (Meader et al., 2010). A trial identified by Tilson et al. (2007) of five sessions of individual CBT to encourage PWID to use non-injecting routes of administration also provided equivocal evidence (Dolan et al., 2004).

In addition to the above studies, Degenhardt et al. (2010) identified a meta-analysis that reported non-significant reductions in needle sharing resulting from behavioural interventions targeted at PWID living with HIV (Crepaz et al., 2006); and a systematic review that reported a reduction in injecting risk behaviour in three of five studies of behavioural interventions (Lyles et al., 2007).

Impact on drug dependence and/or treatment-related outcomes

With regard to CM, Tilson et al. (2007) highlighted that this approach has been reported to be effective in the treatment of stimulant-dependent individuals and in those dependent on opioids alongside other drugs. For instance, CM has been reported to be beneficial for the treatment of methamphetamine dependence (Shoptaw et al., 2005; Shoptaw et al., 2006), although participants were not necessarily injectors of such drugs, and studies have reported that those dependent on opioids and other drugs and receiving MMT and CM had longer periods of abstinence compared to those receiving MMT alone (Peirce et al., 2006a; Petry and Martin, 2002; Piotrowski et al.,

1999b). However, one RCT found no significant benefit of MMT and CM compared to MMT and performance feedback (Schottenfeld et al., 2005).

For individuals dependent on opioids but not receiving OST, evidence suggests that CM may not be an effective treatment. A single study found that the receipt of vouchers and CBT conferred no benefit for treatment retention or opioid-use compared to treatment with CBT alone (Katz et al., 2002) and a systematic review (Mayet et al., 2005) highlighted that insufficient evidence was available to draw firm conclusions regarding the effectiveness of psychosocial interventions alone for the treatment of opiate dependence.

Tilson et al. (2007) concluded:

'No psychosocial intervention alone (in the absence of pharmacotherapies) has been shown to be consistently efficacious in treating opioid dependence.'

The same authors also reported that:

'Strong evidence from a significant number of well-done randomized, controlled trials shows that CM is associated with longer retention in treatment and time abstinent from stimulants among individuals who are primary dependent on stimulants, and among individuals who are dependent on both stimulants and opiates and enrolled in agonist maintenance therapy. CM has not been found to be efficacious for individuals who are addicted to opiates and who are not enrolled in agonist maintenance therapy.'

Summary of evidence

No psychosocial intervention alone has been shown to be effective in relation to reducing injecting risk behaviour and further evidence is needed.

There is insufficient evidence to draw conclusions regarding the effectiveness of any single psychosocial intervention alone in relation to treatment of opiate dependence, although evidence indicates that CM may provide benefit to those dependent on stimulants.

3.1.6 Dihydrocodeine

No reviews were identified that included studies regarding treatment for opioid dependence with dihydrocodeine. However, one RCT carried out in Scotland was identified that examined the effectiveness of dihydrocodeine as an alternative to methadone for the treatment of opioid dependence over a period of 42 months (Robertson et al., 2006). Participants were randomised to receive either methadone mixture of 1 mg/ml or dihydrocodeine as a 30 mg or 60 mg dose. No significant difference was evident between groups with respect to injecting drug use, or for the additional outcomes retention in treatment, or total illicit opiate use.

3.1.7 Detoxification

A supplementary review (Degenhardt et al., 2010) highlighted three studies regarding the impact of detoxification (Amato et al., 2008a; Day et al., 2005; WHO, 2009). Day et al. (2005) examined evidence regarding the effectiveness of inpatient versus other settings for opioid detoxification and identified one study. A larger proportion of study participants in the inpatient group were opioid-free on discharge compared to the outpatient group, but the study concluded that there was insufficient evidence to draw firm conclusions about the outcomes of different settings for detoxification (Day et al., 2005). A systematic review (Minozzi et al., 2009) identified two trials of detoxification methods in young people but also found that there was insufficient evidence to draw conclusions about the effectiveness of detoxification compared to other interventions or no interventions. Moreover, WHO have recommended that inpatient detoxification should be integrated with other drug treatment options, rather than being provided as a stand-alone service, owing to high relapse rates (WHO, 2009).

Summary of evidence

There is insufficient evidence regarding the impact of detoxification on outcomes relating to opiate dependence, HIV or HCV incidence, or injecting risk behaviour.

Summary of evidence regarding non-OST forms of drug treatment in relation to injecting risk behaviour and drug dependence- or treatment-related outcomes

There is limited evidence to draw conclusions regarding the effectiveness of non-OST forms of drug treatment, including individual psychosocial approaches and the combination of OST and psychosocial approaches in relation to injecting risk behaviour. However, there is tentative review-level evidence that the combination of pharmacological and psychosocial treatment is beneficial in relation to compliance, completion of treatment and abstinence at follow-up.

3.2 Impact of pharmacological drug treatment on anti(retro)viral treatment

Evidence regarding the effectiveness of OST in relation to enhanced adherence to ART and virological success of ART (i.e. reduced viral load and raised CD4 T-cell count) was identified in two supplementary reviews (Malta et al., 2008; WHO, 2007b). One core review (Tilson et al., 2007) briefly addressed this topic and identified two studies, one of which was not included in the supplementary reviews (Lucas et al., 2006). Evidence regarding the impact of OST on adherence to ART is covered only briefly in this chapter, but further information can be found in the WHO clinical protocol for the European Region (WHO, 2007a).

The supplementary reviews between them identified seven studies, including four cohort studies (Bouhnik et al., 2002; Clarke et al., 2003a; Moatti et al., 2000; Palepu et al., 2006a). Three of the cohort studies (Bouhnik et al., 2002; Clarke et al., 2003b; Moatti et al., 2000) utilised data from the MANIF2000 cohort study carried out in France, whilst the other used data from a Canadian cohort (Palepu et al., 2006b).

Both Moatti et al. (2000) and Bouhnik et al. (2002) reported that PWID receiving BMT were more likely to be adherent to ART compared to active PWID (AOR non-adherent compared to adherent for active PWID vs PWID receiving BMT: 5.09, 95% CI 1.29–20.13) (Moatti et al., 2000). A cohort study carried out in Ireland also reported a significant association between MMT and adherence to ART in HIV-positive PWID (Clarke et al., 2003b). In support of these findings, an observational study (Tobin et al., 2005) identified in the supplementary review by WHO (2007) reported that directly observed ART provided to those receiving MMT was associated with virological suppression.

An additional cohort study carried out in Canada (Palepu et al., 2006b) demonstrated that HIV and HCV-co-infected PWID receiving MMT showed significantly greater adherence to ART (OR 1.52, 95% CI 1.16–2.00); greater suppression of HIV-1 RNA (AOR 1.34, 95% CI 1.00–1.79); and greater increases in CD4 cell counts (AOR 1.58, 95% CI 1.26–1.99). Lastly, a non-randomised comparative study indicated that a significantly higher proportion of HIV-positive PWID receiving MMT showed virological success receiving DAART compared to those receiving MMT and either standard medical and psychosocial care or treatment adherence support (Lucas et al., 2004).

With regard to the impact of drug treatment on effectiveness of HCV treatment, one supplementary review (Hellard et al., 2009) examined evidence for the effectiveness of HCV treatment in PWID receiving OST. The authors of the review highlight that amongst all studies that included groups of PWID enrolled in drug treatment programmes before initiation of hepatitis C treatment, the median SVR rate was 47.6% (range 27.6–94.1%).

The review identified one retrospective study at a gastroenterology inpatient or outpatient unit in France (Cournot et al., 2004) that compared PWID receiving OST, PWID not receiving OST, former PWID and non-PWID. A larger proportion of PWID receiving OST achieved a sustained virological response (SVR) (35.5% compared to 15.8%, 24.5% and 19.0% respectively) but the difference between groups was not statistically significant.

Two additional studies reported that a larger proportion of PWID receiving OST achieved SVR during treatment with interferon (IFN) or pegylated IFN (pIFN) and ribavirin (RBV) compared to former PWID or non-PWID (IFN and RBV: 47.6% vs. 28.6% vs. 35.9% respectively and pIFN and RBV: 72.2% vs 53.8% vs. 53.8%) although the difference between groups was not significant in either study (Schaefer et al., 2003; Schaefer et al., 2007). Two additional prospective studies reported no significant differences between the proportion of PWID receiving OST that achieved SVR following pIFN and RBV treatment for HCV and the proportion of non-PWID achieving SVR following such treatment (42% vs 56% and 63% vs 77% respectively) (Mauss et al., 2004; Neri et al., 2007).

> ## Summary of evidence regarding the impact of OST on anti(retro)viral treatment
>
> Consistent evidence from multiple studies identified in supplementary reviews indicates that there is tentative review-level evidence for the effectiveness of OST in relation to increased adherence to anti-retroviral therapy and increased virological success of ART in HIV-positive PWID.
>
> Evidence from one supplementary review indicates that there is currently no evidence to suggest that OST is associated with significantly improved virological responses to HCV in PWID.

3.3 Drug treatment for non-opioid dependent PWID

While there is a strong body for evidence supporting the role of pharmacological opioid substitution treatment to reduce the transmission BBVs among PWID, there is a relative lack of sufficient evidence for effective drug treatment approaches to reduce the transmission of infectious disease among people who inject stimulants and other non-opioid substances.

3.3.1 Pharmacological treatment

Tilson et al. (2007) reported that no pharmacological treatments have been found to be consistently efficacious in treating individuals dependent on stimulants in relation to drug use or retention in treatment. However, the impacts of such treatments on the occurrence and/or risk of HCV or HIV were not discussed and whether such individuals were injectors of such stimulants was not specified.

3.3.2 Psychosocial treatment

Degenhardt et al. (2010) identified one systematic review (Knapp et al., 2007) which examined evidence regarding psychosocial treatment for psychostimulant abuse or dependence. No summary estimate of effect was reported owing to the heterogeneity of studies; and for this reason it was also reported that no firm conclusions could be drawn regarding the effectiveness of a single treatment approach in relation to psychostimulant dependence. However, evidence suggested that therapy involving CM was associated with higher rates of abstinence and retention in treatment (Knapp et al., 2007).

CM was also reported to be effective in the treatment of stimulant-dependent individuals in an additional core review (Tilson et al., 2007). Two RCTs demonstrated effectiveness in relation to methamphetamine use (Shoptaw et al., 2005; Shoptaw et al., 2006), as outlined above, and a number of studies demonstrated efficacy of CM with respect to drug use and retention in treatment for those dependent on stimulants (Higgins et al., 1991; Higgins et al., 1993; Higgins et al., 1994; Higgins et al., 2000; Petry et al., 2004) and cocaine (Peirce et al., 2006b). Tilson et al. (2007) also highlighted that there is modest evidence of efficacy of other behavioural approaches, including CBT, community reinforcement with CM and individual counselling, in addressing stimulant misuse. However, whether these drug users injected those substances was not always clear in individual studies. There is weak evidence regarding the impact of motivational interviewing and for the effectiveness of therapeutic communities.

> ## Summary of evidence regarding treatment for non-opiate dependent drug users
>
> There is evidence to support the benefit of CM in relation to drug use or retention in treatment for individuals dependent on stimulants, but evidence relating to other approaches is less clear.

3.4 Service delivery

3.4.1 Settings: Drug treatment in the prison setting

HIV and HCV incidence

Two core reviews (Gowing et al., 2008b; Larney, 2010) included assessment of the impact of prison-based OST on HIV incidence and cited one RCT (Dolan et al., 2003). The RCT of MMT in prison found no difference in HIV incidence between those in MMT and waitlist controls. However, this was in the context of a short period of follow-up, and HIV prevalence was zero at baseline and follow-up, reflecting the low prevalence of HIV in prisons in Australia (Dolan et al., 2003). Two supplementary reviews of prison OST (Stallwitz and Stover 2007; WHO, 2007b) identified the same study (Dolan et al., 2003).

Two supplementary reviews of OST provided in the prison setting (Stallwitz and Stover 2007; WHO, 2007b) identified two linked studies regarding the impact of OST on HCV incidence (Dolan et al., 2003) (Dolan et al.,

2005), one of which is highlighted above. The studies reported no difference in HCV incidence between those receiving MMT and those in the waitlist control group at five-month follow-up (Dolan et al., 2003). However, at four-year follow-up, retention in MMT was associated with reduced HCV infection, and short MMT episodes (less than five months in duration) were significantly associated with greater risk of HCV (Dolan et al., 2005).

In relation to injecting risk behaviour, two supplementary reviews addressed the impact of OST in this regard in the prison setting (Stallwitz and Stover, 2007; WHO, 2007). WHO identified seven studies of prison-based OST (Bayanzadeh et al., undated; Boguña, 1997; Dolan et al., 1996; Dolan et al., 1998; Dolan et al., 2003b; Heimer et al., 2005; Heimer et al., 2006), although some of these studies reported very similar findings from the same data set (e.g. Heimer et al., 2005; Heimer et al., 2006). Stallwitz and Stover (2007) refer to three studies included in the WHO report. All studies demonstrated that PWID receiving MMT in prison injected significantly less frequently compared to those not receiving MMT.

WHO concluded:

'Prison-based OST programmes appear to be effective in reducing the frequency of injecting drug use and associated sharing of injecting equipment, if a sufficient dosage is provided and treatment is provided for longer periods of time' (p. 9).

Summary of evidence

There is insufficient review-level evidence to draw conclusions about the effect of OST on HIV or HCV seroconversion in the prison setting. Data from one RCT in a jurisdiction with low HIV prevalence found no difference in HIV incidence between those receiving MMT and those in the control group; whilst one RCT follow-up study suggests that retention in MMT from prison to community settings is associated with reduced HCV incidence. Further research to assess the effectiveness of OST in preventing infectious disease in prison is warranted.

There is tentative evidence to support the effectiveness of prison-based OST in reducing injecting risk behaviour among PWID by significantly reducing the frequency of injection.

3.4.2 Delivery of OST

The majority of evidence regarding the effectiveness of drug treatment in relation to the occurrence and risk of HIV and HCV relates to OST, thus, service delivery considerations will be discussed only in relation to this form of treatment.

Evidence regarding the optimal dose of OST is provided in two Cochrane reviews (Faggiano et al., 2003b; Mattick et al., 2008). Faggiano et al. (2003) reported that methadone dosages between 60 and 100 mg per day are more effective than lower dosages in relation to retention in treatment and reduction of heroin use during treatment. For treatment with buprenorphine, Mattick et al. (2008) reported that treatment with flexible doses was significantly less effective compared to methadone with respect to retention in treatment (RR 0.82, 95% CI 0.69–0.96). High dose buprenorphine (> 6 mg) is required to significantly suppress heroin use compared to placebo; and low and high doses of buprenorphine was significantly more effective than placebo in relation to retention in treatment (RR 1.24, 95% CI 1.06–1.45; RR 1.21, 95% CI 1.02–1.44). Moreover, it was reported that there was no benefit of treatment with medium dose buprenorphine (7–15 mg) compared with treatment with methadone (at dosages between 60 and 120 mg per day) in terms of retention in treatment or heroin use.

With regard to the duration of OST required to optimise effectiveness of treatment, evidence suggests that continuous treatment is more effective compared to short-term use of OST (Tilson et al., 2007). However, WHO recommend that flexible dosing structures should be encouraged, including a low starting dose and high maintenance dose, without restriction on dosage and duration of treatment (WHO, 2009).

The provision of OST via low-threshold or high-threshold services is an additional consideration. Low-threshold programmes are oriented towards harm reduction rather than abstinence and are more flexible in terms of eligibility requirements and services provided compared to high-threshold programmes. Evidence from the Amsterdam Cohort Study indicates that low-threshold methadone programmes alone may not be sufficient to reduce HIV seroconversion (Hartgers et al., 1992; Langendam et al., 1999; Van Ameijden et al., 1992) but further research is needed.

Summary of evidence

Evidence from one high-quality review demonstrates that methadone doses between 60 and 100mg/day are more effective than lower doses in relation to retention in treatment and reduction in heroin use. High dose (>60mg/day) methadone is more likely to retain patients in treatment and to suppress heroin use compared to high dose (6–12mg) buprenorphine. Evidence indicates that medium or high doses are required to significantly reduce heroin use compared to placebo.

4 Summary of findings

Analysis of the evidence indicates that the majority of studies regarding the prevention of blood-borne viruses (BBVs) in people who inject drugs (PWID) relate to the impact of opioid substitution treatment (OST), with comparatively fewer studies available regarding other forms of treatment. However, there is strong evidence at the level of reviews to support the effectiveness of OST, in particular methadone maintenance therapy (MMT), in reducing HIV transmission and self-reported injecting risk behaviour. There is also moderate evidence which indicates that OST is effective in reducing HCV transmission. Evidence indicates that OST reduces injecting risk behaviour among PWID in prison, but there is insufficient evidence in the prison setting to draw conclusions regarding the impact of OST in reducing HIV or HCV transmission.

There is currently not enough evidence at the level of reviews to draw conclusions regarding the impact of other forms of drug treatment on HIV or HCV transmission or injecting risk behaviour, but moderate review-level evidence supports the use of psychosocial approaches alongside OST in relation to opioid use, compliance, and completion of treatment. There is currently a relative lack of sufficient evidence for effective drug treatment approaches to reduce the transmission of infectious disease among people who inject stimulants and other non-opioid substances. A growing body of evidence demonstrates that the combination of OST and needle and syringe programmes (NSP) is more effective in reducing HIV or HCV incidence and injecting risk behaviour than either approach alone.

In HIV-positive PWID, OST increases adherence to antiretroviral therapy (ART) and, thereby, the likelihood of achieving virological success. However, there is currently not enough review-level evidence to draw conclusions regarding the effectiveness of OST in increasing compliance and/or virological success in response to HCV treatment.

Overall, evidence supports the role of pharmacological opioid substitution treatment in reducing transmission and progression of HIV, and a reduction in the risk of HCV seroconversion, when provided at adequate doses over a sufficient time period.

5 Suggestions for future evaluation research

Based on the evidence reviewed and presented here, several areas have been identified in which more research could be helpful in producing a stronger evidence base to inform future public health decision making and practice. Namely, in the area of drug treatment, while there is a strong body for evidence supporting the role of pharmacological opioid substitution treatment to reduce the transmission blood-borne viruses among people who inject drugs, there is a relative lack of evidence for effective drug treatment approaches to reduce the transmission of infectious disease among people who inject stimulants and other non-opioid substances. Given the high prevalence of stimulant injection and poly-drug use in some European settings, a stronger evidence base is needed in order to determine the most effective approach to infection prevention in these populations. Additionally, a more robust evidence base is needed to evaluate which psychosocial treatment strategies are effective for stimulant injectors, opioid-injectors, or poly-drug users.

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Appendix 1: Search terms

Review of the effectiveness of opioid substitution therapy for the prevention of infectious diseases in injecting drug users.

Search strategies for review-level evidence.

Viral infections: HIV, HCV, HBV

MEDLINE searched via Ovid Gateway:

1	review.pt.
2	exp "review"/
3	exp consensus development conference/
4	exp Meta-Analysis/
5	((review$ or overview$) and (systematic or methodologic$ or quantitative$ or literature$)).tw.
6	1 or 2 or 3 or 4 or 5
7	*Hepatitis c/pc
8	(hepatitis c or hepatitis c virus or hcv).tw.
9	*hepatitis b/pc
10	((hepatitis b or hepatitis b virus or hbv) not vaccination).tw.
11	*HIV infections/pc
12	(HIV or human immunodeficiency virus).tw.
13	Transmission.tw.
14	Seroconver$.tw.
15	8 and 13
16	8 and 14
17	10 and 13
18	10 and 14
19	12 and 13
20	12 and 14
21	Risk behavio?r.tw.
22	risk reduction behavior/
23	behavio?r modification.mp.
24	needle sharing/
25	risk-taking/
26	7 or 9 or 11 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27	*substance abuse, intravenous/
28	(substance$ or drug$).tw.
29	(abuse$ or depend$ or use$ or misus$ or addict$).tw.
30	(inject$ or intravenous).tw.
31	28 and 29
32	28 and 30
33	27 or 31 or 32
34	harm reduction/
35	intervention studies/
36	exp Preventive Health Services/
37	exp Community Health Services/
38	exp primary prevention/
39	34 or 35 or 36 or 37 or 38
40	*methadone/
41	*buprenorphine/
42	(substitution or maintenance).ti,ab.
43	(substitution or maintenance).mp.
44	40 or 41 or 42 or 43
45	39 or 44
46	6 and 26 and 33 and 45
47	limit 46 to (english language and yr="2000 -Current")

Embase searched via Ovid Gateway:

1	review.pt.
2	limit 1 to (english language and yr="2000 -Current")
3	Metaanalys$.ti,ab.
4	limit 3 to (english language and yr="2000 -Current")
5	Meta-analys$.ti,ab.
6	limit 5 to (english language and yr="2000 -Current")
7	((review$ or overview$) and (systematic or methodologic$ or quantitative$ or literature$)).ti,ab.
8	limit 7 to (english language and yr="2000 -Current")
9	2 or 4 or 6 or 8
10	*hepatitis C/pc
11	(hepatitis c or HCV).ti,ab.
12	*hepatitis b/pc
13	((hepatitis b or hbv) not vaccination).ti,ab.
14	*human immunodeficiency virus infection/pc
15	HIV.ti,ab.
16	Transmission.ti,ab.
17	Seroconvers$.ti,ab.
18	Risk behavio?r.ti,ab.
19	((needle$ or syringe$) and sharing).ti,ab.
20	Risk reduction/
21	exp behavior modification/
22	exp high risk behavior/
23	11 and 16
24	11 and 17
25	13 and 16
26	13 and 17
27	15 and 16
28	15 and 17
29	10 or 12 or 14 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30	*substance abuse/
31	(substance$ or drug$).ti,ab.
32	(abuse$ or depend$ or use$ or misus$ or addict$).ti,ab.
33	(inject$ or intravenous).ti,ab.
34	31 and 32
35	31 and 33
36	30 or 34 or 35
37	exp harm reduction/
38	exp intervention study/
39	exp preventive health service/
40	exp primary prevention/
41	exp infection prevention/
42	37 or 38 or 39 or 40 or 41
43	*methadone/
44	*buprenorphine/
45	(substitution or maintenance).ti,ab.
46	43 or 44 or 45
47	42 or 46
48	9 and 29 and 36 and 47

PsycINFO searched via Ovid Gateway

1	evidence based practice (de)
2	limit 1 to (human and english language and "0800 literature review" and yr="2000 -Current")
3	intervention (de)
4	limit 3 to (human and english language and "0800 literature review" and yr="2000 -Current")
5	program evaluation (de)
6	limit 5 to (human and english language and "0800 literature review" and yr="2000 -Current")
7	meta analysis (de)
8	limit 7 to (human and english language and "0800 literature review" and yr="2000 -Current")
9	2 or 4 or 6 or 8
10	drug abuse (de)
11	drug addiction (de)
12	(at risk populations or developing countries) (de)
13	intravenous drug usage (de)
14	10 or 11 or 12 or 13
15	hepatitis c.mp.
16	hiv.mp.
17	Hepatitis b.mp
18	infectious disorders (de)
19	transmission.mp.
20	seroconvert*.mp.
21	needle sharing (de)
22	risk taking (de)
23	risk behavio?r.mp.
24	treatment outcomes (de)
25	exp Health Care Seeking Behavior/
26	health care utilization (de)
27	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28	AIDS prevention (de)
29	harm reduction (de)
30	preventative medicine (de)
31	28 or 29 or 30
32	methadone maintenance (de)
33	buprenorphine.mp.
34	(substitution or maintenance).mp.
35	32 or 33 or 34
36	31 or 35
37	9 and 14 and 27 and 36

CINAHL searched via EBSCO host

ID#	Search Terms
S40	S6 and S22 and S28 and S38
S39	S6 and S22 and S28 and S38
S38	S33 or S37
S37	S34 or S35 or S36
S36	substitution or maintenance.ti,ab.
S35	(MH "buprenorphine")
S34	(MH "methadone")
S33	S29 or S30 or S31 or S32
S32	(MH "community health services+")
S31	(MH "preventive health care+")
S30	(MH "experimental studies+")
S29	(MH "harm reduction")

S28	S23 or S24 or (S25 and S26) or (S25 and S27)
S27	inject* or intravenous.ti,ab.
S26	abuse* or depend* or use* or misus* or addict*.ti,ab.
S25	substance* or drug*.ti,ab.
S24	(MH "intravenous drug users")
S23	(MH "substance abuse, intravenous")
S22	S7 or S9 or S11 or (S8 and S13) or (S8 and S14) or (S10 and S13) or (S10 and S14) or (S12 and S13) or (S12 and S14) or S15 or S17 or S18 or S20 or S21
S21	TI needle sharing or AB needle sharing
S20	(MH health behavior+")
S19	(MH health behavior+")
S18	TI risk behav* or AB risk behav*
S17	risk behav*.ti,ab.
S16	risk behav*.ti,ab.
S15	(MH "Risk taking behavior+")
S14	(MH "seroconversion")
S13	(MH "disease transmission+")
S12	hepatitis b or hepatitis b virus or hbv.ti,ab.
S11	"hepatitis b"/
S10	hiv or human immunodeficiency virus.ti,ab.
S9	hiv infections/
S8	hepatitis c or hcv or hepatitis c virus.ti,ab.
S7	hepatitis c/
S6	S1 or S2 or S3 or S4 or S5
S5	(review* or overview* or evaluation*.ti,ab.) and (systematic or methodologic* or quantitative* or literature*.ti,ab.)
S4	(MH "Meta Analysis")
S3	(MH "Program Evaluation")
S2	(MH "Literature Review+")
S1	systematic review/

Cochrane Library searched via Wiley Online Library [including: Cochrane Reviews, Other Reviews, Clinical Trials Methods Studies, Technology Assessments, Economic Evaluations, Cochrane Groups]

[Excluded clinical trials for #13]

ID	Search
#1	(HCV):ti,ab,kw or (hepatitis c):ti,ab,kw or (hepatitis c virus):ti,ab,kw
#2	(HIV):ti,ab,kw or (human immunodeficiency virus):ti,ab,kw
#3	(HBV):ti,ab,kw or (hepatitis b virus):ti,ab,kw or (hepatitis b):ti,ab,kw
#4	(risk NEXT behav*):ti,ab,kw
#5	(substance*):ti,ab,kw or (drug*):ti,ab,kw
#6	(inject*):ti,ab,kw or (intravenous):ti,ab,kw
#7	(methadone):ti,ab,kw or (buprenorphine):ti,ab,kw
#8	(substitution or maintenance):ti,ab,kw
#9	(#1 OR #2 OR #3 OR #4)
#10	(#5 AND #6)
#11	(#7 OR #8)
#12	(#9 AND #10 AND #11)
#13	(#9 AND #10 AND #11)

Appendix 2: Critical appraisal tool

Author(s):
Title:
Full bibliographic details (including ISSN/ISBN)

List the topic areas with which the review is concerned.

Is the paper best described as (tick as appropriate):
• Systematic review?
• Meta-analysis?
• Synthesis?
• Literature review?
• Other review (please specify)

Does it address (tick as appropriate)?
• Effectiveness (interventions and treatments)
• Causation
• Monitoring and surveillance trends
• Cost
• Inequalities
• Other (please specify)

Does the paper have a clearly focused aim or research question?	Yes	No	Unsure

Consider whether the following are discussed:

• The population studied	Yes	No	Unsure
• The interventions given	Yes	No	Unsure
• The outcomes considered	Yes	No	Unsure
• Inequalities	Yes	No	Unsure

What measures of social difference do the authors use (e.g. class, occupation, socio-economic group, gender, ethnicity, age, residence, geography, disability)?

Do the reviewers try to identify all relevant English language studies?	Yes	No	Unsure
Do the reviewers consider non-English language primary sources?	Yes	No	Unsure

When reviewing articles consider whether details are given of:

• Databases searched	Yes	No	Unsure
• Years searched	Yes	No	Unsure
• References followed up	Yes	No	Unsure
• Experts consulted	Yes	No	Unsure
• Grey literature searched	Yes	No	Unsure
• Search terms specified	Yes	No	Unsure
• Inclusion criteria described	Yes	No	Unsure
• Sensitivity and specificity	Yes	No	Unsure
• What materials were excluded	Yes	No	Unsure
• Whether the data extraction was performed in a systematic way (this is repeated further down)	Yes	No	Unsure
• Whether the criteria used to assess the quality of the primary studies were stated (this is repeated further down)	Yes	No	Unsure

Is the primary source used by the reviewers drawn from:

• Peer-reviewed published materials	Yes	No	Unsure
• Non peer-reviewed published materials	Yes	No	Unsure
• Unpublished materials	Yes	No	Unsure
• Self-referential materials	Yes	No	Unsure

How are reviews rated?

• Do the authors address the quality (rigour) of the included studies?	Yes	No	Unsure

Consider whether the following are used:

• A rating system	Yes	No	Unsure
• More than one assessor	Yes	No	Unsure

Do the authors acknowledge theoretical issues in:

• The materials they have reviewed?	Yes	No	Unsure
• Their own approach?	Yes	No	Unsure

Is the evidence categorised by reviewers?

If the evidence is calibrated, ranked or categorised, what measure/scale is used?

Have the results been combined?

If results have been combined was it reasonable to do so? Consider the following:

• Are the results of included studies clearly displayed?	Yes	No	Unsure
• Are the studies addressing similar research questions?	Yes	No	Unsure
• Are the studies sufficiently similar in design?	Yes	No	Unsure
• Are the results similar from study to study (test of heterogeneity)?	Yes	No	Unsure
• Are the reasons for any variation in the results discussed?	Yes	No	Unsure

Have the data been presented in a way which allows an independent assessment of the strength of the evidence to be made?	Yes	No	Unsure
Can statements made by the reviewers be tracked back to the primary sources precisely (by page number)?	Yes	No	Unsure
Are sufficient data from individual studies included to mediate between data and interpretation/conclusions?	Yes	No	Unsure
Does the paper cover all appropriate interventions and approaches for this field (within the aims of the study)? If no, what?	Yes	No	Unsure

Issues of bias

Does the review make clear what steps have been taken to deal with potential bias? If yes, what are these?	Yes	No	Unsure
Have the authors taken care to avoid double counting of primary data?	Yes	No	Unsure
Do the authors refer to primary research studies in which they themselves have been involved?	Yes	No	Unsure
Do the authors have a vested interest in the direction of the evidence?	Yes	No	Unsure

If bias has not been overtly considered, or only partly considered, what are the potential biases which should have been acknowledged?

To what extent does the treatment of bias in the paper affect any conclusions in it about strengths of evidence?

What is the overall finding of the review? Consider:

• How the results are expressed (numeric – relative risks, etc.)?
• Whether the results could be due to chance (p-values and confidence intervals)?

Do the authors acknowledge any weaknesses in what they have written?

Relevance to developing and transitional populations
Can the results be applied/are the results generalisable to a
developing/transitional country population group?   Yes   No   Unsure

• Are there cultural differences?   Yes   No   Unsure
• Are there differences in healthcare provision?   Yes   No   Unsure
• Is the paper focused on a particular target group
  (age, sex, population sub-group, etc.)?   Yes   No   Unsure

Can a judgement now be made of the review in the following four areas:
• The strengths of the evidence?   Yes   No   Unsure
• The weaknesses in the evidence?   Yes   No   Unsure
• The gaps in the evidence?   Yes   No   Unsure
• The currency in the evidence?   Yes   No   Unsure

Recommended category 1, 2, 3, or discard.

Additional comments:

Reviewer:
Date:

Adapted from: Canning U, Millward L, Raj T, Warm D. Drug use prevention among young people: a review of reviews. London: Health Development Agency; 2004.

Appendix 3: Results

Table A3.1. Summary of studies included in chapter:

Author, date	Title	Terms of Reference/scope	Dates covered	Critical assessment	Studies included
Degenhardt et al. (2010)	Prevention of HIV infection for people who inject drugs: why individual, structural, and combination approaches are needed	Summary of evidence on effectiveness of preventive approaches to HIV infection in PWID	Up to 2009	Supplementary review	4 HIV 12 drug treatment
Gowing et al. (2008)	Substitution treatment of injection opioid users for prevention of HIV infection	Assessment of effect of OST for opioid dependent PWID on rates of HIV infection and high-risk behaviours	Up to July 2003	Core review	5 HIV 24 IRB
Larney S (2010)	Does opioid substitution treatment in prisons reduce injecting-related HIV risk behaviours? A systematic review	Systematic review of evidence on OST in prisons and injecting-related HIV risk behaviours	Dates of literature search not specified. Publication date of included primary studies to 2006	Core review	5 HIV
Sorensen and Copeland (2000)	Drug abuse treatment as an HIV prevention strategy: a review	Systematic review of evidence on whether drug abuse treatment prevents HIV infection	1988–1998	Core review	6 HIV 19 IRB
Stallwitz and Stöver (2007)	The impact of substitution treatment in prisons: a literature review	Review of published and unpublished literature on effectiveness of prison-based OST	1990 to date not specified. Publication dates up to 2006	Supplementary review	4 IRB
Tilson et al. (2007)	Preventing HIV infection among injecting drug users in high-risk countries: an assessment of the evidence	Review of published and unpublished literature on the effectiveness of HIV prevention interventions for PWID	Up to January 2006	Core review	4 HIV 21 IRB 20 other drug treatment
Wright and Tompkins (2006)	A review of the evidence for effectiveness of primary prevention interventions for hepatitis C among injecting drug users	Review of evidence on interventions targeting PWID to reduce prevalence or incidence of HIV	Up to April 2003	Supplementary review	6 HCV
WHO (2007)	Effectiveness of interventions to manage HIV in prisons: opioid substation therapies and other drug dependence treatment	Review of published and unpublished evidence on drug treatment in preventing HIV in prison	No specified. Publication dates up to 2006	Supplementary review	2 HCV 1 HIV 8 IRB

* IRB: injecting risk behaviour

Table A3.2. Summary of reviews regarding OST and ART

Author, date	Title	Terms of reference/scope	Dates covered	Critical assessment	Studies included
Malta et al. (2008)	Adherence to antiretroviral therapy for human immunodeficiency virus/acquired immune deficiency syndrome among drug users: a systematic review	Review of evidence regarding treatment with ART in drug users.	1996–2007	Supplementary review	4 HIV & ART
Tilson et al. (2007)	Preventing HIV infection among injecting drug users in high-risk countries: an assessment of the evidence	Review of published and unpublished literature on the effectiveness of HIV prevention interventions for PWID.	Up to January 2006	Core review	2 OST and ART
Hellard et al. (2009)	Hepatitis C treatment for injecting drug users: A review of the available evidence	Systematic review of studies to evaluate treatment compliance and effectiveness of HCV treatment in PWID.	Up to September 2008	Supplementary	5 OST & HCV treatment