

FINAL DRAFT
MARCH 2005



EVIDENCE FOR ACTION TECHNICAL PAPERS

**EFFECTIVENESS OF DRUG
DEPENDENCE TREATMENT
IN PREVENTING HIV AMONG
INJECTING DRUG USERS**



**World Health
Organization**

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ACKNOWLEDGEMENTS

This document was authored by Michael Farrell, John Marsden, Walter Ling, Robert Ali and Linda Gowing.

WHO would like to thank the many international experts who have provided assistance in the preparation of this review: Professor Mauricio de Lima Pelotas of Brazil, Dr Emilis Subata of Vilnius, Lithuania, Dr Manit Srisurapanont of Chiang Mai, Thailand and Marta Torrens of Barcelona, Spain. Useful comments on early draft were provided by Maristela Monteiro and Vladimir Poznyak, Department of Mental Health and Substance Use, World Health Organization.

The document was developed and edited by Gundo Weiler, Monica Beg, Andrew Ball, Richard Steen and Manuela Moeller under the supervision of Isabelle de Zoysa and Kevin o'Reilly, Department of HIV/AIDS, World Health Organization.

WHO acknowledges the generous contribution of the Australian Agency for International Development (AusAID) to the development of this publication.

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PREFACE

The global environment for a response to HIV has shifted substantially towards a massive scaling up of prevention, treatment and care interventions. In particular, the world made an unprecedented commitment during the United Nations Special Session on HIV/AIDS in 2001 to halting and reversing the epidemic by 2015. In support of this, additional resources to fund an expanded response have become available through the Global Fund to Fight AIDS, Tuberculosis and Malaria.

Countries face the challenge of translating these commitments into practical programmes, including a range of comprehensive interventions to address HIV transmission related to injecting drug use. Although a huge body of scientific literature details the effectiveness of interventions, public health professionals often experience difficulties in accessing and interpreting this knowledge base.

This publication, together with other Evidence for Action Technical Papers, aims to make the evidence for the effectiveness of selected key interventions in EFFECTIVENESS OF DRUG DEPENDENCE TREATMENT IN PREVENTING HIV AMONG INJECTING DRUG USERS accessible to a policy-making and programming audience. The interventions reviewed range from providing information and sterile injection equipment to the impact of drug dependence treatment on HIV prevention. Each publication summarizes the published literature and discusses implications for programming with a particular focus on resource-limited settings.

INTRODUCTION

The significance of HIV lies in the suffering to individuals and families, with premature loss of life and a general burden to the community. It also results in high cost of treatment and care. The introduction of combination anti-retroviral therapy for those infected with HIV has delayed progression to Acquired Immune Deficiency Syndrome (Volberding, 1999), but these drugs are expensive and are not available in all countries. It is not only the spread of HIV/AIDS among injecting drug users that is relevant. Injecting drug users infected with HIV can become a means of transmission to the general population through sexual contacts with people who are not drug users, as well as transmission to unborn children by infected mothers. Links between drug use and commercial sex work are also significant to the spread of HIV beyond the population of injecting drug users.

Injecting drug users are vulnerable to infection with HIV and other blood-borne viruses as a result of collective use of injecting equipment as well as sexual behaviour. The risk of virus transmission through injecting drug use is determined by:

- epidemiological factors (viral load of the infected contact; the way in which injecting equipment is shared; individual susceptibility);
- psychosocial factors (drug craving; intoxication; risk knowledge and attitude towards risk); and
- environmental factors (hurried use in public places; access to clean injecting equipment; and settings, such as prisons, where individual injecting episodes carry a high risk and there is limited access to sterile injecting equipment).

Individuals who are new initiates to injecting are particularly vulnerable to sharing injecting equipment since they may not know how, or may be afraid to inject themselves and frequently ask a more experienced user (who is more likely to be carrying an infection) for assistance. Women also have increased vulnerability because they are more likely to be asked by their partner to share injecting equipment and often find it difficult to negotiate low-risk sexual practices and condom use.

Since sharing or use of contaminated syringes and needles is a very efficient way of spreading HIV, HIV can spread very rapidly among injecting drug users (Des Jarlais, 1992; Stimson, 1995). The recent situation in east Europe demonstrates this very dramatically. For example, in the Russian Federation the number of registered drug abusers (mostly opioid users) rose from 65 000 in 1995 to 270 000 in 2000.

In 1996, seven persons per million inhabitants were registered for the first time as having been infected by HIV as a consequence of injecting drug use. This rate increased to 248 persons per million inhabitants in 2000 (UNDCP, 2002).

Overview

The first section of this report outlines the nature of the interventions that are reviewed.

The second section summarizes the evidence of the effectiveness of drug dependence treatment but places a particular emphasis on injecting and injecting-related risk reduction interventions. The key descriptive longitudinal outcome studies that provide data on the impact of interventions on the transmission of HIV are briefly reviewed.

The third section looks at the experiences of different countries in preventing and containing the spread of HIV among drug users and injecting drug users over the past two decades.

Aim and scope

The aim of this review is to consider the effectiveness of drug dependence treatment in preventing HIV among injecting drug users. It is one of a number of reviews of public health strategies for HIV prevention that have the overall aim of providing the best currently available evidence as to the value and benefit of different interventions to reduce the risk of HIV transmission. As such, this paper aims to provide guidance on the effectiveness of interventions for injecting drug users, in the context of a strategic approach to the prevention of HIV/AIDS.

All types of drugs that are commonly injected (heroin, cocaine, amphetamines) and all forms of drug treatment (agonist pharmacotherapy, abstinence-based and behavioural interventions, either alone or in combination with pharmacotherapy) are within the scope of this review.

Consideration was given to only focussing on strategies that have a direct impact on injecting drug use, such as agonist pharmacotherapy. However, it is our view that while such treatment is critical to the task of HIV prevention among injecting opioid users, the other available treatments form an important bedrock to the overall treatment and HIV-prevention strategy. From that point of view all forms of treatment should be considered, since all forms of treatment have some impact on risks of HIV transmission.

Review methodology

This review draws on prior, significant reviews of drug dependence treatment in the prevention of HIV/AIDS, as well as original studies of the effectiveness of drug dependence treatment in terms of preventing the transmission of HIV. Research literature considered for the review was based on the search strategy outlined below.

The most direct means of assessing prevention of HIV transmission would be to consider seroprevalence among injecting drug users in and out of treatment, and rates of seroconversion. However, such studies are few in number and are potentially confounded by factors such as differences in the background prevalence of HIV in the community from which study participants are drawn, as well as additional factors such as access to drug treatment, preventive education and clean injecting equipment, all of which will influence exposure to HIV, thereby influencing seroprevalence and seroconversion rates. Consequently, this review places most emphasis on the effect of treatment on behaviours associated with high risk of HIV transmission, namely injecting drug use, sharing of injecting equipment, the number of sex partners, and unprotected sexual activity.

Multiple electronic databases, including Medline, PsycINFO and EMBASE, were searched using key terms, adjusted according to the indexing system of each database. The reference lists of retrieved reviews and original studies were checked for relevant studies.

Studies included in the review assessed the effectiveness of drug dependence treatment in terms of outcomes relevant to risk of HIV transmission (seroprevalence, seroconversion, injecting behaviour and sexual behaviour). Studies that did not include a comparison (either by differing treatment status, or before/after treatment commencement) were excluded from the review.

1. TREATMENT OF DRUG DEPENDENCE

1.1 Objectives of treatment

The objective of drug dependence treatment is the achievement and maintenance of physical, psychological and social well-being through reducing the risk-taking associated with drug use, through reducing levels of drug use, or through complete abstinence from drug use. Because of the chronic relapsing nature of drug dependence, and the need to address social and psychological dimensions, achieving abstinence is often a lengthy and difficult process for many people. The provision of “stepping stones” or “stabilizing strategies” in the form of short-term and more achievable goals helps to define and structure progress and also to reduce drug-related harms, one of which is the transmission of blood-borne viruses such as HIV, Hepatitis B and Hepatitis C.

The potential impact of drug dependence treatment on preventing HIV is via:

- ▶ reduced injecting drug use;
- ▶ reduced sharing of injecting equipment;
- ▶ reduced risk behaviours related to sexual transmission of HIV; and
- ▶ opportunities for HIV education and medical care (Sorensen & Copeland, 2000).

1.2 Approaches to treatment

Approaches to the treatment of drug dependence are generally organized to blend together a range of different treatment modalities but may be simply categorized as psychosocial (abstinence-based or behavioural interventions) or pharmacological in nature, and can be divided into detoxification, relapse prevention and treatments to reduce drug craving and drug use.

1.2.1 Agonist pharmacotherapy programmes

Programmes of this type entail prescribing a drug with a similar action to the drug of abuse (an “agonist” in pharmacological terms), but with a lower degree of risk. Agonist pharmacotherapy programmes are available only for drug users who are primarily opioid-dependent. Although some researchers and commentators have called for developing agonist pharmacotherapies for cocaine and amphetamine users, currently such approaches are not available.

Agonist pharmacotherapy programmes are of two general types. In detoxification programmes, doses of the agonist will be reduced over a period of time until a drug-free state has been reached. Substitution or maintenance programmes prescribe higher doses of agonist for longer periods of time (six months or more).

The value of substitution or maintenance treatment lies in the opportunity it provides for dependent drug users to reduce their exposure to risk behaviours and stabilize in health and social terms before addressing the physical adaptation dimension of dependence. The principle of substitution treatment is to use standard medication in place of the drug of abuse using a drug that has a longer duration of action, thereby delaying the emergence of withdrawal and reducing the frequency of administration and stabilizing the individual both physiologically and psychologically. The effect is also to reduce the extent to which normal life activities are disrupted by the need to obtain and administer drugs. The provision of medication potentially helps users to move into a stable and structured approach to their life that can enable significant reduction in risk-taking and also in criminal behaviour.

The agent that has been most widely applied, and researched, for agonist pharmacotherapy of opioid dependence is methadone. Typically administered orally as a syrup, a single dose of methadone in most (but not all) people will prevent withdrawal symptoms for 24 hours. Hence, methadone decreases the frequency and intensity of the cycle of intoxication and withdrawal. In maintenance treatment methadone doses of 60 mg/day or more have been identified as being most effective in terms of retention in treatment and reductions in illicit drug use and criminal behaviour (Kreek, 2000; Ward et al., 1998b). However, lower doses are typically used in detoxification regimens (Gowing et al., 2000).

A drug that is emerging as an alternative to methadone for substitution treatment of opioid dependence is buprenorphine, (Mattick et al., 1998a). Buprenorphine is a partial opioid agonist but has enough morphine-like action to substitute for heroin, prevent withdrawal symptoms and reduce craving. Furthermore, with increasing doses, the degree of respiratory depression and other opioid effects reaches a plateau—consequently buprenorphine appears to have less overdose risk associated with it. Buprenorphine’s prolonged duration of action enables it to be administered less frequently (on alternate days). Buprenorphine is not well absorbed

if taken orally—the usual route of administration for substitution treatment is sublingual (under the tongue). It is used widely in France and is currently the subject of considerable research, in both maintenance and detoxification regimens. It has recently been approved by the Food and Drug Administration in the United States of America for use in office-based practice in that country.

1.2.2 Abstinence-based treatment

Abstinence-based or drug-free treatment approaches vary considerably in their setting (outpatient, residential, self-help group) and orientation (Swindle et al., 1995).

Residential rehabilitation is based on the principle that a structured, drug-free residential setting provides an appropriate context to address the underlying causes of addictive behaviour. These programmes assist the client in developing appropriate skills and attitudes to make positive changes towards a drug-free way of life. Therapeutic communities represent a subset of residential rehabilitation defined by the emphasis placed on accepting personal responsibility for decisions and actions (Swindle et al., 1995), and the use of the community as a method to promote the health, welfare and growth of the individual (De Leon, 2000).

Self-help or mutual support groups are generally based on the principles of Alcoholics Anonymous (AA) or Narcotics Anonymous (NA), which espouse a disease concept of drug and alcohol dependency with the promise of recovery, but not cure, for those who adhere to it. The “12 steps” of AA/NA contain a strong spiritual emphasis. They emphasize the importance of reconstructing relationships with other people, which includes confession, restitution, and an injunction to help other alcoholics or addicts. One of the benefits of self-help or mutual support groups is that they provide a mechanism to promote alternative social networks that do not support drug use. It has been found that abstinence is more likely in individuals who have formed new social networks (Powell & Taylor, 1989).

Residential rehabilitation originally was based around lengthy periods of stay. However, in the last two decades, short-term residential rehabilitation programmes have emerged. There is also a developing trend for both therapeutic community and 12-step approaches to be used in conjunction with other treatment approaches (both pharmacological and psychosocial). This diversity of intervention approach complicates the task of assessing the

effectiveness of general drug-free approaches. However, it highlights that in modern treatment systems there is an increasing level of integration across a wide range of treatment modalities and treatment philosophies.

1.2.3 Behavioural interventions

Behavioural interventions may be delivered in the context of abstinence-based treatments or in conjunction with pharmacological approaches. The provision of psychosocial support and counselling to encourage behavioural and emotional change is important to the overall process of treating drug dependence. Psychosocial interventions support the process of lifestyle adjustment, approaches to reduce risk behaviour, and developing skills to cope with factors that could trigger drug use, or to prevent an occasional lapse from becoming a full-blown relapse to regular drug use.

Psychological conditioning is considered to play a large role in the initiation and continuation of drug use, with the euphoric effects of drugs acting as a strong positive reinforcement for further use. Behavioural interventions seek to modify drug-related behaviour by extinguishing conditioning, or by providing strategies to avoid or manage drug-related cues that are part of conditioning.

Behavioural interventions may be delivered in conjunction with pharmacotherapies such as a blocking agent. A blocking agent (an “antagonist” in pharmacology terms) stops the drug of dependence from having an effect, thus removing the euphoria and other positive effects. An example is naltrexone, an opioid antagonist, which blocks the effect of heroin and other opioid drugs.

If drug users are exposed to drug-related cues without the positive reinforcement of euphoria, (and possibly with the negative reinforcement of an aversive agent), over time, drug-seeking behaviour and craving are extinguished (Tucker & Ritter, 2000).

Aversive agents are under consideration for the treatment of cocaine dependence, but are not currently available.

Behavioural interventions are also important to address risk behaviours associated with drug dependence, including injecting practices and sexual behaviour. As such, behavioural interventions delivered in conjunction with drug treatment are important to the prevention of HIV transmission.

2. EVIDENCE OF EFFECTIVENESS

Research on the utility of drug dependence treatment as an HIV-prevention strategy has focussed primarily on methadone maintenance treatment rather than other modalities such as residential or outpatient drug-free treatment (Sorensen & Copeland, 2000). Of 33 studies reviewed by Sorensen & Copeland, 28 included methadone maintenance treatment as a modality, and usually as the only treatment modality.

2.1 Agonist pharmacotherapy programmes

2.1.1 Methadone

From a review of the literature addressing the impacts of methadone maintenance on HIV/AIDS and infectious hepatitis, Ward et al. (1998a) concluded that there is considerable evidence that methadone maintenance programmes protect treatment recipients from HIV/AIDS. This evidence comes from early studies comparing groups in methadone maintenance treatment with the general population of untreated drug users, in addition to several more recent studies.

From a meta-analysis of studies, Marsch (1998) concluded that methadone maintenance treatment has a moderate but significant effect on illicit opiate use ($r=0.35$), and a small to moderate effect on HIV risk behaviours ($r=0.22$).

From a review of 33 studies published in peer-reviewed journals from 1988 to 1999, with an aggregate of 17 771 subjects, Sorensen & Copeland (2000) concluded that there is clear evidence that methadone maintenance treatment reduces HIV risk behaviours, particularly HIV infection. This is based on 26 of 28 studies involving methadone maintenance treatment showing positive results in reducing HIV infection and risk behaviours. They noted that there is less definitive evidence that methadone maintenance treatment reduces needle-sharing and unsafe sexual behaviour.

Methadone maintenance does not completely eliminate heroin use among clients but it does substantially reduce use. Kreek (2000) states that methadone maintenance treatment, with adequate doses of medication and access to counselling as well as medical and psychiatric care as needed, lead to voluntary, one-year retention of 60% to 80% with a reduction of daily illicit opioid use from 100% of people entering treatment to less than 20% of

people within one year. From a review of research literature, Ward et al. (1998b) found that methadone dose showed a positive linear dose–response relationship with retention in treatment and a negative linear relationship with heroin use.

As part of a recent randomized, controlled trial, Schottenfeld et al. (1997) administered methadone at doses of 65 and 20mg/day. They found the higher dose to be significantly better than the lower dose for reducing illicit drug use—the proportion of toxicology tests that was positive for opioids was 45% for the 65mg group compared to 72% for the 20mg group. In a similar study Strain et al. (1999) compared high-dose (80-100mg/day) with moderate-dose (40-50mg/day) methadone. They also found the high-dose regimen to be associated with significantly lower rates of opioid-positive urine samples.

Mattick et al. (2002a), from a systematic review, concluded that methadone appeared statistically significantly more effective than non-pharmacological approaches in retaining patients in treatment (RR=3.05, 95% CI: 1.75-5.35) and in the suppression of heroin use (RR=0.32, 95% CI: 0.23-0.44). Data from observational studies also indicate that methadone maintenance produces better outcomes than detoxification alone, or drug-free treatment in terms of heroin use, criminal behaviour and risky sexual behaviour (Hall et al., 1998). The Treatment Outcomes Prospective Study (TOPS) found that retention in treatment at three months was highest for methadone maintenance treatment (65%), followed by therapeutic communities (44%) and outpatient drug-free treatment (40%). Both methadone maintenance and therapeutic community treatment were associated with reductions in drug use (Hall et al. 1998).

There are also data indicating that methadone maintenance treatment has a secondary preventive effect on the progression of AIDS. Weber et al. (1990) followed a cohort of 297 current and former injecting drug users, all of whom were HIV seropositive but asymptomatic and had similar CD4+ counts at entry to the study. During follow-up (median 16 months) 80 subjects adhered to a programme of methadone maintenance treatment, 124 continued injecting drug use and 93 remained free of illicit drugs. The authors found a significantly lower probability of progression of HIV disease in both the methadone treated group (RR 0.48) and former drug users (RR 0.66) than in persistent injecting drug users (RR 1.78). The overall death rate was significantly higher in persistent injecting drug users, largely due to heroin overdose.

2.1.2 Buprenorphine

Johnson (1997) in a review of clinical trials of buprenorphine in the United States concluded that, in terms of retention in treatment and proportion of opioid-positive urine samples, buprenorphine, at doses between 4 and 16mg/day, is more efficacious than a placebo and equivalent to methadone at doses between 20 and 60mg. In a systematic review, Mattick et al. (2002b), found no advantage for high-dose (6-12mg) buprenorphine over high-dose (60-80mg) methadone in retention (RR=0.79, 95% CI: 0.62-1.01) and high-dose buprenorphine was inferior in suppression of heroin use. Buprenorphine was found to be statistically significantly superior to placebo medication in retention of patients in treatment at all dose levels, but only high and very high doses of buprenorphine suppressed heroin use significantly above placebo. Two other recent meta-analyses have also found relative equality of methadone and buprenorphine in terms of retention in treatment and suppression of heroin use (West et al., 2000; Barnett et al., 2001).

Strain et al. (1996) compared outcomes for a 16-week maintenance phase of a double-blind randomized controlled trial using buprenorphine (N=43) or methadone (N=43). A flexible dosing approach was adopted resulting in mean maintenance dose of 9.0mg/day for buprenorphine and 54mg/day for methadone. The study found few differences in outcomes for the two treatments. Both groups showed decreased illicit opioid and cocaine use. The buprenorphine group showed a trend towards decreasing illicit opioid use over time, while the methadone group stabilized after about four weeks of treatment.

Fischer et al. (1999) also compared buprenorphine and methadone maintenance treatment in a randomized controlled trial (unblinded). In this study, 29 participants received buprenorphine (mean dose of 7.5 mg/day) and 31 participants received methadone (mean dose 63 mg/day). The scheduled duration of treatment was 24 weeks. The authors reported a significantly better retention rate in the methadone group, but those completing the study in the buprenorphine group had significantly lower rates of illicit opiate use.

Schottenfeld et al. (1997), as part of a randomized controlled trial, administered buprenorphine at 4 or 12mg/day. The proportion of toxicology tests that were positive for opioids was 77% for the 4 mg/day group compared to 58% for the 12mg/day group.

(This compared with 45% for a group given 65mg/day of methadone, and 72% for a group given 20mg/day methadone.) This is consistent with other studies in demonstrating the greater effectiveness of higher doses of buprenorphine. The authors found no significant difference in retention rates for the two-dose regimens of buprenorphine.

2.2 Antagonist pharmacotherapy (naltrexone) for opioid dependence

Despite the low level of side effects, patient acceptance of naltrexone is poor (Brahen et al., 1984; Kreek, 2000; Tucker & Ritter, 2000; Zador et al., 1999). Retention rates are highest for highly motivated participants (Brahen et al., 1984; Tucker & Ritter, 2000; Washton et al., 1984).

Tucker and Ritter (2000) identify three studies that found that craving, assessed by self-report, is reduced by naltrexone administration, although there were individual differences between participants in these studies. The reduction in craving is reflected in reductions in opioid use: across six studies identified by Tucker and Ritter (2000) the percentage of opioid-positive urine tests during naltrexone treatment ranged between 2.7 and 10.3%.

Tucker and Ritter (2000) note that the highest rates of post-treatment abstinence occurred in highly motivated participants. For example, Cornish et al. (1997) reported 8% opioid-positive urine samples in parolees and probationers after six months of naltrexone treatment, while Washton et al. (1984) reported 100% of physicians and 64% of business executives were abstinent at 12 months after naltrexone treatment. This compares with rates of 31 to 53% at 12 months for "more usual" participants (Tucker & Ritter, 2000).

The limitations of research evidence relating to the use of naltrexone for relapse prevention treatment of opioid dependence are such that it is currently not possible to draw firm conclusions as to its effectiveness (Kirchmayer et al., 1999; Tucker & Ritter, 2000).

An aspect of concern that is yet to be resolved is the possibility that opioid users treated with naltrexone may be more likely to overdose if they return to heroin use because of the loss of tolerance. Associated depression may also have an impact on

suicide rates. At this stage the degree of risk is difficult to assess because, to date, only one study (Miotto et al., 1997) has reported deaths in the 12 months following naltrexone treatment.

2.3 Pharmacological approaches for cocaine users

No pharmacological intervention has been found to be consistently superior to placebo for the treatment of cocaine dependence (Schuckit, 1994; da Lima et al., 2000).

2.4 Behavioural interventions

In their review of opioid dependence treatment, Mattick et al. (1998b) concluded that psychosocial therapy cannot be considered a stand-alone treatment for opiate dependence. Only 5% to 30% of long-term heroin addicts respond to abstinence-based treatment (Kreek, 2000). However, Mattick et al. concluded there was reasonable evidence that psychosocial therapy adds to the overall effectiveness of methadone maintenance programmes. For example, McLellan et al. (1993) in a randomized controlled trial, compared minimum methadone maintenance treatment (methadone with emergency counselling and referral only) with methadone maintenance treatment plus basic counselling (regular counselling using contingency management) and enhanced methadone (regular counselling plus social work, family and employment counselling). They found that minimum methadone maintenance treatment was associated with a higher rate of opiate-positive urine samples than the basic counselling group, and that enhanced services reduced the rate further.

From a meta-analysis of controlled trials, Griffith et al. (2000) found that contingency management interventions (i.e. the use of incentives and disincentives) are effective in reducing positive urine samples in methadone maintenance treatment (weighted mean effect size 0.25).

The effectiveness of different types of psychological therapy for cocaine use has been found to be variable, possibly reflecting differences in treatment intensity (American Psychiatric Association, 1995) or quality (Crits-Christoph et al., 1999).

Cognitive-behavioural interventions have not generally been demonstrated to be superior to other

psychotherapies in initiating abstinence, but research suggested that its effects may be more durable and thus protective against relapse. Furthermore, it may be more effective with more severely dependent users (Carroll, 1998).

Psychosocial treatments for psychostimulant dependence appear to have a significant impact on outcomes with increased rates of abstinence and reduced numbers of days used, however there is little available evidence to indicate that one approach is superior to another except possibly for contingency counselling that appears to have a treatment-specific effect. Overall, the current data indicate a significant non-specific psychotherapeutic effect for the broad range of psychosocial interventions.

2.5 Abstinence-based drug dependence treatment

There have been very few comparative studies of the outcomes of therapeutic community (TC) treatment with good control of bias and confounding factors, making it difficult to form an accurate view of the effectiveness of this approach relative to other treatment modalities. However, Gowing et al. (2002), in a recent review, formed a view of TC effectiveness by looking at the consistency of outcome for the multiple follow-up studies that are available.

There is a long-standing view that three months or more in treatment is necessary for enduring behavioural change. The studies reviewed by Gowing et al. indicate that between 30% and 50% of those entering TCs remain in treatment at around the three-month mark. Median or mean lengths of stay reported range from 54 to 100 days. Hence the majority of those entering TCs do not remain in treatment for the length of time considered necessary for enduring change. Some strategies, such as preparatory interventions prior to entry, have the potential to improve retention rates, as do approaches such as providing additional services to meet individual needs, but perhaps the strongest message from the reported retention rates is that the TC approach does not suit all people, and individuals are likely to vary in their receptiveness to the approach at different stages of substance abuse and recovery. This emphasizes the importance of linking TCs to other treatment approaches to ensure there are alternatives available for those who find themselves unable to complete treatment.

As with other forms of treatment, relapse to substance use is common following TC treatment. Nonetheless, overall levels and frequency of drug use are significantly reduced by TC treatment, with the reduction still apparent one to two years after exit. The degree of reduction is at least similar to, and possibly more enduring than the changes achieved with methadone maintenance treatment. There is a value in considering this approach as part of overall HIV prevention since all of those who achieve long abstinence dramatically reduce their risk profile for both injecting and drug-related deaths. However, this needs to be balanced by the risks that arise when individuals relapse to chaotic and dependent drug use.

There is a strong indication from studies that time in treatment is a significant determinant of treatment outcome, but this is a complex issue with time being something of a proxy indicator for engagement, participation and progress in treatment.

Self-help or mutual support groups are generally based on the principles of Alcoholics Anonymous (AA) or Narcotics Anonymous (NA). The “12 steps” of AA/NA contain a spiritual emphasis and stress the importance of reconstructing relationships with other people, which includes confession, restitution, and an injunction to help other alcoholics or addicts. One of the perceived benefits of self-help or mutual support groups is that they provide a mechanism to promote alternative social networks that do not support drug use. It has been found that abstinence is more likely in individuals who have formed new social networks (Powell & Taylor, 1989).

AA is the oldest and the most well-known and utilized treatment intervention for alcohol dependence.

Fiorentine and colleagues (Fiorentine, 1999; Fiorentine & Hillhouse, 2000) have used a longitudinal study of more than 400 adult clients entering 25 outpatient treatment facilities in Los Angeles to investigate a number of aspects of 12-step programmes, with attempts to control for the confounders of motivation and simultaneous activities. In this group the primary drugs most commonly used in the year prior to treatment were crack cocaine (56%), cannabis (46%), methamphetamine (24%) and cocaine (22%), with around half the cohort being polydrug users. Key findings were:

- weekly or more frequent 12-step participation may be an effective step in maintaining relatively long-term abstinence;

- less than weekly participation does not seem to be any more effective than non-participation;
- formal drug treatment and 12-step programmes were seen as integrated recovery activities, rather than alternatives;
- participants with pre-treatment involvement in 12-step programmes stayed in treatment longer and were more likely to complete a formal 24-week treatment programme;
- participants who participated in both formal drug treatment and a 12-step programme had higher rates of abstinence than those who participated only in formal treatment (consistent with findings that intensity and duration of treatment is important for a successful outcome).

Weiss et al. (1996) make the point that attending self-help groups in itself is not sufficient—it is participation in self-help group meetings that is critical. They support this view with data from a survey of 519 cocaine-dependent people entering a psychotherapy study. In the week prior to study entry, 34% had attended a self-help group. Of those who attended and actively participated in a self-help group meeting, 55% initiated abstinence within the next month, compared with 40% of non-attenders and 38% of non-participating attenders. Weiss et al. comment that those who attended, and particularly those who participated in self-help group meetings, could be viewed as having entered the “action” stage of change, whereas those who had not attended were likely to be at an earlier stage. (Section 3.1 discusses stages of change.)

2.6 Factors influencing outcomes

The underlying risk of HIV infection may differ in various subgroups of injecting drug users. For example, in a cohort of 91 male drug users (around half currently in treatment) Kelley & Petry (2000) found that on a lifetime measure of drug risk behaviours, those with an antisocial personality disorder reported higher rates of intravenous drug use, frequency of needle-sharing, and number of equipment-sharing partners and lower rates of needle-cleaning. On a measure of past-month risk behaviours, those with anti-social personality disorder reported higher rates of intravenous drug use and lower rates of needle-cleaning. Avants et al. (2000) also note previous research with addicted popula-

tions reporting that concurrent psychiatric difficulties are related to risk-taking behaviour.

In a cohort of methadone maintenance clients, benzodiazepine users were found more likely to have injected recently, had used more amphetamine and cocaine, and had used more drug classes in the month preceding interview. In addition, benzodiazepine users were significantly more likely to have recently both borrowed and lent used needles. The relationship between benzodiazepine use and higher rates of drug use and risk-taking was maintained even though benzodiazepine users had been in treatment longer and were on higher methadone doses (Darke et al., 1993).

The effectiveness of agonist pharmacotherapy for opioid dependence in reducing the risk of HIV infection may also be reduced by concomitant injecting use of cocaine. For example, in a study of injecting drug users currently in methadone maintenance treatment, Bux et al. (1995) found that cocaine users were significantly more likely to report injecting a drug in the previous month than non-users (85% versus 23%) and reported a greater mean number of drug injections (22.5 versus 3.7). Camacho et al. (1996) reported a gender and cocaine use effect for use of 'dirty works' at least once in the prior 30 days.

2.7 Key studies relating drug dependence treatment to HIV prevention

2.7.1 Seroprevalence

A number of studies have reported lower prevalence of HIV antibodies among IDUs in methadone maintenance treatment (Capehorn & Ross, 1995), but because of potential confounding factors, the extent to which the lower seroprevalence is due to participation in methadone maintenance treatment is unclear. The situation regarding seroprevalence is also complicated by HIV-positive status often resulting in preferential entry to MMT.

Tidone et al. (1987) found that patients who started MMT more recently showed a significantly higher incidence of HIV infection than patients in other subgroups (8/13 positive versus 13/61, $p < .01$) suggesting that methadone treatment may help in preventing HIV diffusion. They also found a strong, positive correlation between HIV seropositivity and

positive urinalysis for morphine metabolism, an indication of continued heroin use.

2.7.2 Seroconversion

There are relatively few studies of seroconversion rates, probably because of the large numbers of participants and long periods of time required for such studies to achieve statistical significance.

In an 18-month follow-up study of injecting drug users in and out of methadone maintenance treatment, Metzger et al. (1993) recorded seroconversion rates of 3.5% for those in treatment, compared to 22% for those not in treatment. Williams et al. (1992) found that 2% of a sample who had been in treatment continuously seroconverted, compared to 19% of those who interrupted their treatment.

Moss et al. (1994) report on a cohort of 681 injecting drug users entering methadone maintenance treatment or detoxification who were HIV negative on their first visit and who had at least one further HIV test over a five-year period. Of 145 injecting drug users, 11 (7.6%) with less than 12 lifetime months of methadone maintenance treatment seroconverted, compared to 11/536 (2.1%) with 12 or more lifetime months of methadone maintenance treatment. For those first tested on admission to methadone maintenance treatment, the HIV seroconversion rate was 1.4 per person-years of follow-up (95% CI 0.7-2.4) while for those recruited at admission to detoxification it was 3.1 per person-years of follow-up (95% CI 1.6-5.3).

Langendam et al. (1999) followed a cohort of 582 clients of methadone maintenance treatment in Amsterdam (60% male, 75% with a history of injecting). The total follow-up time was 1906 person-years, with 58 participants seroconverting during follow-up. The incidence of HIV was 6.0 per 100 person-years among current injectors and 0.2 per 100 person-years among non-injectors. There was no clear association between methadone dose or frequency of programme attendance and seroconversion. This indicates it is cessation of injecting drug use rather than methadone maintenance treatment per se that protects against HIV. However, it is also clear that oral methadone treatment is a critical part of the process of change from injecting to non-injecting drug use.

2.7.3 Injecting drug use

Saxon et al. (1994), from an observational follow-up study, identified ongoing risk to be associated with continued use of psychoactive substances, less time in drug dependence treatment during the 18-month follow-up interval, having a sexual partner who was an IDU and not using a drug store (pharmacy) as the primary source of syringes.

White et al. (1994) investigated the injecting behaviour and risky needle use of a sample of methadone maintenance clients. The majority of the sample (116/193) reported injecting one or more drugs in the month prior to data collection. The mean (\pm SD) adjusted prescribed methadone dose was significantly higher for non-injectors (55.5 ± 21.3 mg cf 47.5 ± 17.8 mg). As assessed by Addiction Severity Index composite scores, injectors had significantly more severe drug problems (scaled score, mean \pm SD, 0.55 ± 0.4 cf 0.09 ± 0.09). The level of knowledge of contracting HIV from needle use was very similar for injectors and non-injectors. Non-injectors, on average, were older, and had been in the methadone programme for longer.

Reductions in injecting drug use occur early in the course of methadone maintenance treatment. Brooner et al. (1998) followed two cohorts of new admissions to methadone maintenance treatment, one referred from needle exchange services and one from "standard" sources. Injecting drug use was higher among the cohort referred from needle exchange services. In the 30 days prior to admission, this cohort reported injecting drug use on a mean of 24.08 days. At one-month follow-up, this had dropped to a mean of 13.70 days.

Kwiatkowski compared cohorts of drug users receiving HIV risk reduction interventions with or without methadone maintenance treatment. In the 30 days prior to the baseline interview, the cohort receiving both risk reduction and methadone maintenance treatment reported a mean of 77.1 ± 39.9 heroin injections, compared to 60.1 ± 37.4 for the cohort receiving only risk reduction. At the six-month follow-up, the equivalent data were 22.9 ± 35.9 and 36.3 ± 44.5 . Hence, both cohorts had reduced their HIV risk behaviour, but the reduction was greater for the cohort receiving MMT.

Methadone maintenance treatment reduces both the proportion of drug users who inject and the frequency of injection. Camacho et al. (1996) report HIV risk behaviour data for a cohort of opioid users admitted to three methadone maintenance

programmes as part of the Drug Abuse Treatment and AIDS Reduction (DATAR) study, and who were retained in treatment at three and six months. At intake to methadone maintenance treatment all reported injecting drug use in the 30 days prior to interview. At three months, 59% reported injecting, and at six months it was 53%. At the same time points the mean injection frequencies were 111 ± 59.5 , 7 ± 18.3 and 6 ± 19.3 .

High rates of relapse to drug use following cessation of treatment mean that, in general, reductions in HIV risk are greatest while injecting drug users remain in substitution treatment. This is supported by the finding by Williams et al. (1992) of higher rates of seroconversion among those with interrupted rather than continuous methadone maintenance treatment. Further evidence comes from a study by Britton (1994) of cohorts of injecting drug users who ceased methadone maintenance treatment due to funding cuts, or who remained in methadone maintenance treatment. In this study HIV risk behaviour was assessed one month after notification had been given of the impending funding cuts, and then one year later, at which time the defunded cohort had been out of methadone maintenance treatment for about six months. The mean (\pm SD) days of heroin-injecting in the six months prior to baseline assessment was 18.64 ± 35.64 for the cohort remaining in methadone maintenance treatment, and 56.05 ± 82.68 for the defunded cohort. At the 12-month assessment the equivalent figures were 11.66 ± 27.13 and 82.70 ± 76.22 , respectively. The difference in baseline values provides a degree of confounding but nonetheless the difference between the 2 cohorts at 12 months and the change over time were statistically significant.

2.7.4 Sharing of injecting equipment

In the comparison of cohorts remaining in or ceasing methadone maintenance treatment (see above) Britton (1994) also assessed needle-sharing behaviour. The mean (\pm SD) days of needle-sharing in the six months prior to the baseline assessment was 13.51 ± 28.56 for the cohort remaining in methadone maintenance treatment and 24.93 ± 32.18 for the defunded cohort. At the 12-month assessment the equivalent figures were 0.51 ± 1.22 and 39.07 ± 77.46 , with the change over time statistically significant.

The cohort of new admissions to methadone maintenance treatment followed by Brooner et al. (1998) reported a mean of 4.63 days with sharing of injecting equipment in the 30 days prior to admission.

After one month of treatment this had dropped to a mean of 1.93 days.

Among the cohort of opioid users admitted to methadone maintenance treatment reported by Camacho et al. (1996), 60% reported having used dirty works in the 30 days prior to intake interview. This reduced to 15% at month three, and 15% at month six.

The reduced risk of HIV infection through needle-sharing identified by Caplehorn & Ross (1995) disappeared when methadone patients who had not injected in the month prior to interview were excluded from the analysis, suggesting that respondents in methadone maintenance were at reduced risk of HIV infection because they were less likely to inject drugs.

White et al. (1994) examined injectors in more detail by comparing those whose injections did or did not place them at risk for HIV (by sharing needles, not cleaning or ineffective cleaning). Safe and risky injectors did not differ in terms of time on the programme or adjusted methadone dose, or on any of the Addiction Severity Index composite scores. However, safe injectors had significantly greater knowledge of means of preventing the spread of HIV than risky injectors.

Findings of Longshore et al. (1993) indicate that the relationship between treatment and reduced likelihood of needle-/syringe-sharing is not simply an artefact of reduced injection frequency. However, they were unable to attribute a causal process.

2.8 Major observational studies of treatment outcomes

Large-scale observational studies have had an important impact on our knowledge and understanding of treatment and the treatment process because they have measured the impact of treatment in real-life settings across large geographical areas and across a wide range of types of treatment settings. While these studies do not enable us to calculate treatment effect sizes in comparison with no treatment, they do enable us to have some idea of what sort of impact and outcome we can expect from arranging treatment in such a fashion. These studies also allow us to monitor changes in patterns of presentation and patterns of drug use in those

presenting for help. What is most striking is that a series of large cohort studies have been conducted each decade for the past three decades: the Drug Abuse Research Programme (DARP) in the 1970s, the Treatment Outcome Prospective Study (TOPS) in the 1980s and the Drug Abuse Treatment Outcome Study (DATOS) in the 1990s, all in the United States, and the National Treatment Outcome Research Study (NTORS) in the 1990s in the United Kingdom. The outcomes reported by these studies have been remarkably consistent.

In these studies clients are assessed on the same key outcome measures, and over the same time intervals: before (at baseline or intake to treatment), during and after they complete the programme(s) of interest. These studies provide the capacity to evaluate treatment systems where clients engage in multiple treatments of varying intensities and duration, to show if the desired client outcomes are achieved and to identify which clients change most or least. They can also show how outcomes vary with the amount or type of treatment received. However, because they do not control for many other factors that might explain the changes observed (e.g. non-treatment factors, maturation, cyclical changes), these observational studies cannot definitively show that any observed changes were caused by the treatment(s) of interest.

The two most recent studies (DATOS in the United States and NTORS in the United Kingdom) report on the impact of injecting and other related HIV risk-taking behaviour, which shows significant reductions over time.

In DATOS all modalities of treatment are reported to significantly reduce injecting risk behaviour; retention in treatment is demonstrated to be linked to greater reductions in risk behaviour but also lower baseline rates of risk-taking behaviour. In the DATOS cohort it is clear that the injecting risk-taking behaviour profile of those entering methadone treatment is significantly different from those entering residential and community-based, drug-free treatment, where there were higher rates of cocaine and crack users and non-injectors. These descriptive outcome studies, while pragmatic, cannot control for the inevitable selection bias that arises as a result of these baseline differences in treatment populations.¹

In NTORS, a subsection of the total cohort was followed up for five years. The majority of the original cohort had used drugs intravenously prior to

¹ www.datos.org

treatment. The rate of injecting fell from 60% at intake to 37% at four to five years follow-up, and the rate of self-reported sharing fell from 14% to 5%. These results apply to clients admitted to both community-based methadone treatment and residential treatment.

Overall, these large cohort studies consistently report a significant impact of treatment on behaviour related to injecting drug use. It is clear that for some individuals injecting is eliminated, but for many the impact of the treatment is to reduce the frequency of the behaviour and to reduce the rate of sharing behaviour and thereby reduce the risk of transmission of HIV.

3. PUBLIC HEALTH EXPERIENCE

PUBLIC HEALTH EXPERIENCE OF CONTAINING THE SPREAD OF HIV AMONG INJECTING DRUG USERS

Globally, the story of HIV spread among injecting drug users unfolds rapidly. It has had major potential negative public health consequences for many countries, including China, Estonia, India, Myanmar, the Russian Federation and Ukraine. There has been a rapid spread of injecting drug use to many countries that were previously thought to be safe from such public health problems.

This evolving problem has occurred in settings where there are major infrastructural problems around public health and health-care delivery. Poverty and resource limitation and sometimes political instability make responding to this challenge particularly difficult. Despite a significantly growing drug problem in most settings, there have been notable successes in limiting the spread of HIV among injecting drugs in some areas and in containing the spread where an epidemic has occurred. A range of country experiences are presented here to exemplify issues. They are meant to be neither representative nor comprehensive in their description.

Hong Kong Special Administrative Region (Hong Kong SAR) has a long-standing problem with heroin dependence and has well-established methadone programmes as part of a multi-modal approach to treatment. It is one of the few countries in that region with a long-standing drug substitution programme and, as such, demonstrates that it is possible to deliver this type of treatment in a variety of cultural settings. The current low rates of HIV in Hong Kong SAR also indicate the value of such treatment in containing HIV in injecting drug using populations. Drug trends have been relatively stable except for a more recent increase in psychostimulant use. The methadone treatment programme is voluntary. There are 21 clinic sites in all, with an average of 7000 patients attending for daily methadone. Patients are also able to access voluntary in-patient detoxification and residential rehabilitation services. There is a volunteer peer outreach project that aims to promote risk-reduction behaviour. By the end of 2000, 32 injecting drug users who were HIV positive were identified and this made up 2% of all identified HIV cases in Hong Kong SAR. A social cost study was conducted in 1998, which reported that over

HK\$ 4000 was spent on demand-reduction policies of which 14% was for treatment and rehabilitation and 2.5% on medical care. The study concluded that the money spent on demand reduction was a sound investment, which, overall, reduced public expenditure on drug problems (Chien et al., 2002).

In contrast, in the People's Republic of China, Chengzheng et al. (2002) report that there has been a major growth in the number of addicts and there are now an estimated 0.86 million registered addicts, representing a 12-fold growth over the past decade. Because of the size of China there is considerable regional variation in patterns and trends. The trends in HIV spread are alarming, with a rapid spread of HIV among injecting drug users—it is estimated that two thirds of new HIV cases are among drug users. Treatment relies on detoxification and compulsory labour camps, and the relapse rate is reported to be 80% within two weeks and 95% within six months of discharge (Chengzheng et al., 2002).

A WHO review of Opiate Pharmacotherapy in the Asia Pacific region (2002) notes that many countries are facing a major problem of HIV infection among injecting drug users, but few have mobilized the use of drug substitution as part of the overall response to the problem. Thailand has used short-term methadone and reports high rates of HIV in injecting drug users, however, overall reports a stable-but-high seroprevalence of HIV among injecting drug users (Perngarn, Jittiwutikarn, 2002). Nevertheless, a major epidemic of methamphetamine use is causing serious problems within Thai society and within the country's health, social welfare and criminal justice services, and potentially could have a major impact on the hitherto successful containment of the heterosexual HIV epidemic in Thailand. Other countries, such as Indonesia, Malaysia, Myanmar and Viet Nam, report high rates of HIV among injecting drug users (WHO, 2002).

Kumar (2002) reports that 90% of the world's opium is produced in Asia, and it is estimated that 60% of the world's opiate users live in Asia. Injecting drug use is reported as one of the major forces driving the HIV epidemic in many Asian countries (Kumar,

2002). Overall, Kumar argues that most programmes in Asia lack quality coverage that would ensure a good mixture between treatment availability, community outreach, including access to sterile syringes, interventions in the criminal justice system and approaches to promoting sexual health and reducing sexually transmitted diseases. Kumar describes a programme of opiate maintenance with buprenorphine in five cities in India—Calcutta, Chennai, Imphal, Mumbai and New Delhi—and reports that evaluation indicates a positive influence in reducing injection-related HIV risk behaviours among participating drug users with additional benefits such as reduction in criminal behaviour and improved psychosocial functioning. However, there is limited support for such programmes and there is major difficulty in financing their expansion and continuation.

Australia initiated methadone treatment early and expanded it rapidly as a part of a strategy to contain HIV. The incidence of HIV among injecting drug users in Australia is reported to be very low, with levels below 1%. By contrast, many of the other Western Pacific Region countries are in a different stage of development and problem recognition. For many countries injecting drug use is a relatively new problem and they face the difficulty of recognizing and responding to a new and complex social problem with the development of culturally appropriate services. In addition, the challenge of HIV and injecting drug use involves creating a broader network of public health responses. These appear to require time for both authorities and the general public to understand the practical and pragmatic necessity of such approaches without appearing to condone drug use and injecting drug use.

The experience in Europe has been well described and tracked through the European Monitoring Centre on Drugs and Drug Abuse. The growth in the provision of drug substitution services has been mirrored by a reduction in the incidence of AIDS cases related to injecting drug use in most European Union (EU) countries. The link between these trends is complex but overall there is now reasonable data to support the case that at an individual level, substitution treatment, along with other harm-reduction measures, is an effective component of HIV prevention. There has been a major expansion in services with a convergence in approaches to the organization of services. Most EU countries now aim to provide a broad and comprehensive spectrum of services ranging from basic community access, to more structured community approaches, to detoxifi-

cation and maintenance pharmacotherapy and, to a more limited and varied extent, in-patient and residential rehabilitation services. The countries with high incidence of HIV, such as Italy, France and Spain, have successfully contained the epidemic of the late 1980s. Most other countries report that HIV seroprevalence among injecting drug users ranges from 1% to 15%. Farrell et al. (2000) reported on the high level of provision of methadone and other opioid agonists and concluded that such treatment is one of a number of critical components of a comprehensive HIV-prevention strategy for injecting drug users.

In central and eastern Europe and in the new independent states there has been a rapid spread of heroin and injecting drug use in the past decade. Injecting drug users constitute a major proportion of those testing HIV positive in most of these countries. A number of countries have established drug substitution treatment and others are currently putting such services in place. In many countries there is a shortage of available material and personnel as well as general resources, and the challenges facing many of these countries are quite considerable where they have a wide range of competing health priorities. In particular, a major outbreak of HIV in Estonia, the Russian Federation and Ukraine has caused major public health concern and indicates a need for new expansion of treatment and prevention approaches.

The United States was the initial evaluator and pioneer of large-scale methadone treatment programmes in the early to mid-1970s and there is now a very broad range of treatment options in the country for the management of drug dependence. A lack of public funding mechanisms at local and state level has limited the comprehensiveness of approaches in differing localities, however, overall there has been a substantial containment of HIV among injecting drug users in the United States. A similar picture prevails in Canada, where levels of HIV among injecting drug users are low with some outbreaks reported in British Columbia and Montreal.

Where there is a strong commitment to vigorous enforcement of drug prohibition laws and a strong commitment to abstinence-based treatments with substantial levels of providing long-term residential rehabilitation or other forms of long-term enforced institutional treatment for drug dependence there can be deep resistance to starting pharmacologically based treatments for opioid dependence.

A significant number of countries in the Eastern Mediterranean Region and the Western Pacific Region invest heavily in correctional facilities for individuals who use illegal drugs. There is a need to move towards a more mixed approach to the configuration of services in these countries so that more community-based and accessible services can be provided to a larger population of problematic and dependent drug users who are in need of support and advice.

Virtually all of the above has focussed on injecting opiate use, but in many countries psychostimulants are also injected and present a significant risk for the spread of HIV. In addition, the smoking of psychostimulants such as methamphetamine and crack cocaine are associated with a range of high-risk behaviours, and there is a substantial group who undergo transition from smoking to injecting drug use. The use of crack cocaine in South America and the current evolving availability of heroin has presented a challenge for HIV containment amidst a wide range of social problems.

4. CONCLUSIONS AND RECOMMENDATIONS

Overall, in many countries there has been substantial success in containing the spread of HIV among injecting drug users. It is important to note that where there is an aim of providing a comprehensive and varied range of treatment services there appears to be more success in containing the spread of HIV.

All countries with a population of heroin or injecting drug users should aim to develop a comprehensive range of treatments and these treatments should include drug substitution maintenance treatment for opioid dependence. Policy-makers need to be clear that the development of drug substitution treatment is a critical component of the HIV prevention strategy among injecting opioid users.

Research on cost effectiveness by Gossop and colleagues reports that in the NTORS study there was a 3-fold savings in social and health-care costs for every single unit of spending, indicating an overall cost benefit from treatment. An earlier study in the United States returned a similar finding, reporting a 7-fold saving for every single unit cost of expenditure when criminal justice and other costs were incorporated.

There is a need to look at costs and expenditure within different social and cultural settings, but currently there is a major expenditure in many countries on imprisonment and prolonged incarceration in detention centres, approaches that are associated with very high relapse rates soon after release. There is no evidence to indicate that such an approach is cost effective and much to indicate that comparative cost-effectiveness evaluations need to be conducted if and when new pilot projects on agonist pharmacotherapy are started in some countries.

Countries with forced institutional long-term treatment should review their overall treatment strategy and look to redeploy resources from such institutions into community-based drug substitution treatment programmes.

Overall, opiate agonist pharmacotherapy remains controversial and there are many authorities who are very resistant to the use of such treatments. International evidence needs to be translated into local action and further evaluations are required to achieve an impact on policy-makers and providers. Currently, the epidemic spread of HIV in the Western Pacific Region and also in parts of eastern Europe and the Russian Federation requires urgent shift in

policy in order to contain the spread of HIV among injecting drug users. There is likely to be continued controversy and resistance to the use of such treatment. For this reason a continued rigorous, critical and impartial approach to the benefits of such treatment needs to be made on an ongoing basis. However, policy-makers also need to be made aware of the very high costs of not putting such treatment in place. Countries without such treatment are those currently reporting major HIV outbreaks and such negative trends are likely to continue.

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