PREVENTING HIV INFECTION AMONG INJECTING DRUG USERS IN HIGH-RISK COUNTRIES

AN ASSESSMENT OF THE EVIDENCE

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

PREVENTING HIV INFECTION AMONG INJECTING DRUG USERS IN HIGH-RISK COUNTRIES

AN ASSESSMENT OF THE EVIDENCE

Committee on the Prevention of HIV Infection Among Injecting Drug Users in High-Risk Countries

Board on Global Health

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

THE NATIONAL ACADEMIES PRESS 500 Fifth Street, N.W. Washington, DC 20001

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the Committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This study was supported by Contract No. 39417 between the National Academy of Sciences and the Bill & Melinda Gates Foundation and by Contract No. HQ-05-413065 between the National Academy of Sciences and the Joint United Nations Programme on HIV/AIDS. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

International Standard Book Number-10: 0-309-10280-4 (Book)
International Standard Book Number-13: 978-0-309-10280-3 (Book)
International Standard Book Number-10: 0-309-66343-1 (PDF)
International Standard Book Number-13: 978-0-309-66343-4 (PDF)

Additional copies of this report are available from the National Academies Press, 500 Fifth Street, N.W., Lockbox 285, Washington, DC 20055; (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area); Internet, http://www.nap.edu.

For more information about the Institute of Medicine, visit the IOM home page at: **www.iom.edu.**

Printed in the United States of America.

The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Advising the Nation. Improving Health.

THE NATIONAL ACADEMIES

Advisers to the Nation on Science, Engineering, and Medicine

The **National Academy of Sciences** is a private, nonprofit, self-perpetuating society of distinguished scholars engaged in scientific and engineering research, dedicated to the furtherance of science and technology and to their use for the general welfare. Upon the authority of the charter granted to it by the Congress in 1863, the Academy has a mandate that requires it to advise the federal government on scientific and technical matters. Dr. Ralph J. Cicerone is president of the National Academy of Sciences.

The **National Academy of Engineering** was established in 1964, under the charter of the National Academy of Sciences, as a parallel organization of outstanding engineers. It is autonomous in its administration and in the selection of its members, sharing with the National Academy of Sciences the responsibility for advising the federal government. The National Academy of Engineering also sponsors engineering programs aimed at meeting national needs, encourages education and research, and recognizes the superior achievements of engineers. Dr. Wm. A. Wulf is president of the National Academy of Engineering.

The **Institute of Medicine** was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under the responsibility given to the National Academy of Sciences by its congressional charter to be an adviser to the federal government and, upon its own initiative, to identify issues of medical care, research, and education. Dr. Harvey V. Fineberg is president of the Institute of Medicine.

The **National Research Council** was organized by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and advising the federal government. Functioning in accordance with general policies determined by the Academy, the Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing services to the government, the public, and the scientific and engineering communities. The Council is administered jointly by both Academies and the Institute of Medicine. Dr. Ralph J. Cicerone and Dr. Wm. A. Wulf are chair and vice chair, respectively, of the National Research Council.

www.national-academies.org

COMMITTEE ON THE PREVENTION OF HIV INFECTION AMONG INJECTING DRUG USERS IN HIGH-RISK COUNTRIES

HUGH TILSON (*Chair*), University of North Carolina School of Public Health, Chapel Hill, NC
APINUN ARAMRATTANA, Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand
SAMUEL A. BOZZETTE, The RAND Corporation, Santa Monica, and the University of California San Diego School of Medicine, La Jolla, CA
DAVID D. CELENTANO, Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD
MATHEA FALCO, Drug Strategies, Washington, DC
THEODORE M. HAMMETT, Abt Associates Inc., Cambridge, MA
ANDREI P. KOZLOV, Biomedical Center and St. Petersburg University, St. Petersburg, Russia
SHENGHAN LAI, Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD
AJAY MAHAL, Department of Population and International Health, Harvard University School of Public Health, Boston, MA
RICHARD S. SCHOTTENFELD, Yale University School of Medicine, New Haven, CT
SUNITI SOLOMON, Centre for AIDS Research and Education, Y.R. Gaitonde Medical Educational and Research Foundation, Chennai, India

Staff

ALICIA R. GABLE, Study Director
ALYSON SCHWABER, Senior Program Associate
SHEYI LAWOYIN, Senior Program Assistant
PATRICK KELLEY, Board Director

Consultants

SANDRA HACKMAN, Editor
LESLIE PRAY, Writer

Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's (NRC's) Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible, and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

Richard Ashcroft, Queen Mary, University of London, Barts and the London Medical and Dental School, Institute of Health Sciences Education, United Kingdom
Constance A. Benson, AIDS Clinical Trials Group and Antiviral Research Center, University of California San Diego
Chris Beyrer, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD
Robert E. Booth, University of Colorado School of Medicine, Denver, CO
Lawrence O. Gostin, Georgetown University Law Center, Washington, DC, and Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD
Marc N. Gourevitch, New York University School of Medicine

Martin Iguchi, RAND Drug Policy Research Center, Santa Monica, California and University of California Los Angeles School of Public Health
Adeeba Kamarulzaman, University of Malaya Medical Center, Kuala Lumpur, Malaysia
Kenneth Mayer, Brown University Medical School and the Miriam Hospital, Providence, RI
A. Thomas McLellan, Treatment Research Institute, Philadelphia, PA
Harold Pollack, University of Chicago School of Social Service Administration
Vu Minh Quan, Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand and Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD
David Vlahov, New York Academy of Medicine

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by **Arthur L. Reingold,** Professor and Head, Division of Epidemiology, University of California, Berkeley; and **Floyd Bloom,** Chairman and Professor, Department of Neuropharmacology, The Scripps Research Institute, La Jolla, CA. Appointed by the National Research Council and Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures, and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring Committee and the institution.

Acknowledgments

The Committee recognizes the tremendous efforts of several individuals whose contributions invigorated discussions at its meetings and enhanced the quality of this report. The Committee extends its most sincere gratitude to all those mentioned below.

The Committee thanks the sponsors of this study, Joint United Nations Programme on HIV/AIDS (UNAIDS) and the Bill and Melinda Gates Foundation. Special recognition goes to Anindya Chatterjee, Arminda Dayupay, Marie-Therese Drahamcha, David Haroz, Michael Iskowitz, Mahesh Malingham, Purnima Mane, Peter Piot, and Barbara de Zalduondo, at UNAIDS and David Allen and Todd Summers at the Gates Foundation for their extra effort and repeated attention in providing information and support for the study.

The Committee appreciates the testimony of the following individuals at its December 2005 meeting: Andrew Ball, Chris Beyrer, Saulius Caplinskas, Monica Ciupagea, Roel Coutinho, Don Des Jarlais, Ksenia Eroshina, Michael Farrell, Loon Gangte, Peter Ghys, Tomas Hallberg, Catherine Hankins, Lily Hyde, Adeeba Kamarulzaman, Kerstin Kall, Christian Kroll, Alexey Mazus, Samuel Nugraha, Peter Piot, Gerry Stimson, Raminta Stuikyte, Oleg Tchestnov, Inga Upmace, Nikolay Volodin, Alex Wodak, George Zazulin, and Fugie Zhang. The agenda for the information-gathering workshop in which these individuals participated appears in Appendix A.

The Committee would also like to express its gratitude to those who shared their extensive knowledge on this topic: Chris Buchner, Don Des

Jarlais, Ross Gibson, Herman Joseph, Richard Needle, Pascale LeClerc, Carole Morissette, and Daniel Wolfe.

The Committee would be remiss if it did not also acknowledge the hard work and dedication of the study staff from the Board on Global Health. We would like to thank Alicia Gable, study director, for her commitment to ensuring that the report would be of the highest-possible quality. To Alyson Schwaber, senior program associate, the Committee extends its gratitude for her outstanding ability to understand and analyze the research. Sheyi Lawoyin, senior project assistant, did a great job coordinating the logistics of the study. Patrick Kelley, the director of the board, was an extremely valuable resource. In addition, the Committee thanks IOM staff members Matt Solyst and Chelsie Benca for their assistance in preparing the report. Special appreciation goes to writer Leslie Pray and editor Sandra Hackman for their instrumental services. The Committee sincerely thanks research librarians Bill McLeod (IOM) and Roberta Shanman (the RAND Corporation) for assisting the Committee with literature searches. The Committee would also like to thank several consultants who assisted the Committee during the literature review: Sarah Lewis, Katherine McLean, Adriana Van Breda, and Maya Yiadom.

Contents

TABLES, FIGURES, AND BOXES

Tables

Figure

Boxes

Acronyms and Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
AOR	Adjusted Odds Ratio
ART	Antiretroviral Treatment
ASPD	Anti-Social Personality Disorder
ATS	Amphetamine Type Stimulants
CBT	Cognitive Behavioral Therapy
CI	Confidence Interval
CM	Contingency Management
CRA	Community Reinforcement Approach
DAART	Directly Administered Antiretroviral Therapy
DATOS	Drug Abuse Treatment Outcome Studies
ESAP	Expanded Syringe Access Program
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IDU(s)	Injecting Drug User(s)
IOM	Institute of Medicine
LAAM	Levo-Alpha-Acetyl-Methadol

MMT	Methadone Maintenance Treatment
MSIC	Medically Supervised Injecting Center
NA	Narcotics Anonymous
NADR	National AIDS Demonstration Research Program
NIDA	National Institute on Drug Abuse (U.S.)
NIMH	National Institute of Mental Health (U.S.)
NSE	Needle and Syringe Exchange
OR	Odds Ratio
RCT	Randomized Control Trial
RR	Relative Risk
SIF	Supervised Injecting Facility
STI	Sexually Transmitted Infection
TC	Therapeutic Communities
TSF	Twelve-Step Facilitation
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNODC	United Nations Office on Drugs and Crime
VCT	Voluntary Counseling and Testing
WHO	World Health Organization

Summary

Drug dependence is a complex, chronic, relapsing condition that is often accompanied by severe health, psychological, economic, legal, and social consequences (IOM, 1990, 1995). It is manifested by a complex set of behaviors including compulsive drug craving, seeking, and use that interferes with an individual's physical, mental, and social functioning (IOM, 1997; McLellan et al., 2000). Similar to other chronic conditions, such as heart disease or diabetes, individuals with drug dependence can stabilize their condition by making behavioral changes and with the use of appropriate medications (WHO et al., 2004). Drug-dependent individuals have high rates of medical and psychiatric comorbidity and increased risk of premature mortality (DHHS, 2006). Injecting drug users are particularly vulnerable to HIV and other bloodborne infections (such as hepatitis C) as a result of sharing contaminated injecting equipment. All drug-dependent individuals, including injecting drug users (IDUs), may be at increased risk of HIV infection because of high-risk sexual behaviors.

There are an estimated 13.2 million injecting drug users worldwide—78 percent of whom live in developing or transitional countries (Aceijas et al., 2004). The sharing of contaminated injecting equipment has become a major driving force of the global AIDS epidemic and is the primary mode of HIV transmission in many countries throughout Eastern Europe, the Commonwealth of Independent States,[1] and significant parts of Asia (UNAIDS,

[1]The Commonwealth of Independent States includes Azerbaijan, Armenia, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Russia, Tajikistan, Turkmenistan, Uzbekistan, and Ukraine.

2006). In some cases, epidemics initially fueled by the sharing of contaminated injecting equipment are spreading through sexual transmission from IDUs to non-injecting populations, and through perinatal transmission to newborns. Reversing the rise of HIV infections among IDUs has thus become an urgent global public health challenge—one that remains largely unmet.

STUDY GOALS AND APPROACH

In response to this challenge, in 2005 the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the Bill & Melinda Gates Foundation commissioned the Institute of Medicine to undertake an expedited review of the scientific evidence on strategies to prevent HIV transmission through contaminated injecting equipment, with a specific focus on high-risk[2] countries—namely in Eastern Europe, the Commonwealth of Independent States, and significant parts of Asia—where injecting drug use is, or is on the verge of becoming, the primary driver of the HIV epidemic.

The charge to the Committee included five questions. They are listed here in the order in which they are addressed in the chapters. The Committee found it most helpful to first discuss the evidence on the intermediate outcomes of drug-related risk (question one) and sex-related risk (question two) prior to examining the impact on HIV transmission (question three).

1. What impact do needle and syringe exchange, disinfection programs, drug substitution programs, drug treatment programs, and counseling and education have on the extent and frequency of drug injection?
2. What evidence is there on the extent to which these prevention strategies help reduce HIV transmission from IDUs to their sex partners and through maternal-to-child transmission to their offspring?
3. How effective are such programs in reducing HIV transmission among IDUs?
4. To what extent do such programs also increase the use of health and social services and drug treatment?
5. What evidence is there that programs aimed at reducing the risk of HIV transmission among IDUs are more effective when they are part of a comprehensive array of services, which include outreach, HIV prevention education, counseling, referral to drug substitution treatment, drug rehabilitation services, and medical and psychosocial support?

[2]In this report, such countries are labeled as "high-risk," indicating that injecting drug use is, or is on the verge of becoming, the primary driver of the HIV epidemic.

In response to this charge, the Committee convened a public workshop in Geneva, Switzerland, in December 2005 to gather information from experts on IDU-driven HIV epidemics in the world's most affected regions (see Appendix A for the meeting agenda). The Committee also conducted a comprehensive search of the English language peer-reviewed scientific literature, and evaluated previous systematic reviews and reports prepared by international organizations (see Appendix B for further detail on the Committee's review methods). To assess this evidence, the Committee held a closed meeting in Washington, DC, in March 2006, and also conducted numerous conference calls.

Although the report focuses on HIV prevention for IDUs in high-risk countries, the Committee considered evidence from countries around the world. The findings and recommendations of this report are also applicable to countries where injecting drug use is not the primary driver, but in which injection drug use is nevertheless associated with significant HIV transmission.

HIV PREVENTION STRATEGIES FOR IDUS

This report focuses on programs designed to prevent the transmission of HIV among IDUs. These programs range from efforts to curtail nonmedical drug use to those that encourage reduction in high-risk behavior among drug users. The term "harm reduction" is often used to describe programs such as sterile needle and syringe access, because their primary aim is to reduce the harms related to drug use among those who are unable or unwilling to stop using drugs. However, because the term has a wide range of interpretations, the Committee refers to all interventions in this report as HIV prevention programs for IDUs.

The Committee grouped the wide range of HIV prevention strategies for IDUs into three categories: (1) drug dependence treatment, which include both pharmacotherapies and psychosocial interventions; (2) sterile needle and syringe access; and (3) outreach and education programs (see Box S-1). Other HIV prevention strategies, such as voluntary counseling and testing, antiretroviral therapy, and prevention and treatment of sexually transmitted infections, are important for IDUs but also apply to broader populations. While there is a large body of evidence evaluating the effectiveness of these interventions, the Committee's review was limited to those prevention interventions specific to IDUs. Therefore, Chapter 1 includes only a brief overview of these broader interventions.

The most effective way to reduce the risks of HIV transmission among injecting drug users is to stop drug use. However, not all drug users are ready or able to take this step. An individual IDU's risk of HIV infection is mediated by both individual-level factors (such as severity of dependence

BOX S-1 Key HIV Prevention Interventions for IDUs

Drug treatment—pharmacotherapies

Two primary types of pharmacotherapies are available for treating opioid dependence: agonist agents and antagonist agents. No pharmacotherapies have been found to be consistently efficacious in treating stimulant dependence.

Opioid agonist maintenance medications work by preventing withdrawal symptoms and reducing opioid cravings—and therefore the need to use illicit drugs—and also by diminishing the effects of opioid use by creating cross-tolerance to their effects (IOM, 1995). Agonist medications have two primary clinical applications: they can be used on a limited basis to facilitate opioid detoxification,[a] or they can be administered over a longer period as a maintenance treatment (IOM, 1995). This report focuses on the latter application. In maintenance therapy, the agonist agent is administered at higher doses for a sustained period. The goal of maintenance treatment is to reduce illicit drug use and high-risk behavior by building cross-tolerance to the effects of other opioids, thereby allowing patients to stabilize physiologically and psychologically, so they can reengage in normal life activities (IOM, 1990; WHO et al., 2004). Due to their long half life and resulting steady state, opioid agonists are not intoxicating and do not impair function when used at clinically appropriate and stable doses over time (IOM, 1990, 1995). Methadone, a full opioid agonist, is the most widely used and researched agonist maintenance medication for the treatment of opioid dependence (WHO et al., 2004). Buprenorphine is a partial opioid agonist that is used increasingly as an alternative to methadone. Both methadone and buprenorphine are classified as psychotherapeutic medicines for substance dependence treatment programs on the World Health Organization (WHO) list of essential medicines (WHO, 2005c). Other pharmacological agonist agents have been studied in limited settings, but are not widely used and are not reviewed in this report (MacCoun and Reuter, 2001; WHO et al., 2004).

An alternative to opioid agonists are antagonist agents that block the effects of opioids. Naltrexone, the most widely used opioid antagonist, helps patients maintain long-term abstinence from opioids (WHO, 2005a). Oral naltrexone provides a relatively long-lasting blockade (1 to 3 days, depending on the dose) of euphoric or rewarding effects of heroin or other opioids, and thus may help prevent resumption of opioid use (O'Brien and Kampman, 2004). New long-acting, injectable formulations of naltrexone produce adequate opioid blockade for up to 1 month (Dunbar et al., 2006). Before beginning naltrexone treatment, patients must be detoxified (medically withdrawn from heroin or other opioids), because naltrexone will precipitate severe withdrawal symptoms in people physically dependent on opioids (O'Brien and Kampman, 2004).

Drug treatment—psychosocial

A second major approach to drug treatment involves psychosocial interventions, which include a broad range of psychological and behavioral strategies, used either alone or in combination with pharmacotherapies and other medical or social interventions (Mayet et al., 2004). These interventions may be provided with varying levels of intensity, frequency, and duration, using different approaches including outpatient, partial hospital, hospital, or residential-based programs. Psychosocial interventions may be delivered in individual or group settings, and may also include family members in order to address family functioning (e.g., through behavioral family therapy). Examples of psychosocial interventions include specific behavioral interventions (e.g., cognitive behavioral therapy, contingency management) as well as collection of program models (e.g., therapeutic communities, 12-step programs) (see Chapter 2, Box 2.2 for a description of these interventions).

Sterile needle and syringe access

Sterile needle and syringe access may include needle and syringe exchange; the legal, accessible, and economical sale of needles and syringes through pharmacies, voucher schemes, physician prescription programs, or vending machines; supervised injecting facilities or rooms; and disinfection programs.

In most cases, needle and syringe exchange (NSE) is part of a multi-component HIV prevention effort. The Committee uses the term "multi-component HIV prevention programs that include needle and syringe exchange" to refer to programs that combine NSE with one or more of the following services: outreach, health education in risk reduction, condom distribution, bleach distribution coupled with education on needle disinfection, and referrals to substance abuse treatment and other health and social services.

Outreach and education

Outreach and education rely on peers and local health workers to identify IDUs and provide education on preventing HIV infection, and to serve as guides to health and social services (WHO, 2004a). Outreach workers may distribute information on HIV/AIDS, bleach kits for disinfecting injection equipment, and condoms. While some programs are linked to needle and syringe exchanges or drug treatment clinics, outreach efforts often occur outside clinical settings and separate from other interventions.

---

[a]Detoxification refers to medically supervised withdrawal to a drug-free state over a short period of time (typically 5–7 days, but up to several months). When used to assist with detoxification, the agonist agent helps to relieve patient discomfort during withdrawal and the dosage is slowly tapered over time until the person reaches a drug-free state (IOM, 1990; 1995). Detoxification alone is not considered an effective treatment (IOM, 1990). Studies show users have high rates of relapse to drug use when detoxification is not followed by further therapeutic intervention (IOM, 1990).

and co-existing psychiatric disorders) and structural-level, or environmental, factors (such as drug laws and law enforcement and socioeconomic stability) (Rhodes et al., 2005). The vast majority of HIV prevention efforts target the risk behavior of individual drug users (Rhodes et al., 2005), for example, through drug treatment or outreach. Structural-level interventions, which attempt to create an environment supportive of individual behavioral change, have received less attention from researchers and policymakers (Rhodes et al., 2005; Burris et al., 2004). Examples of structural-level interventions include legal reform and programs to reduce stigma and discrimination against HIV-infected people and drug users.

CONCLUSIONS ON THE EFFECTIVENESS OF HIV PREVENTION INTERVENTIONS

The Committee's major conclusions and key recommendations regarding the five questions in the charge follow (see Box S-2 for a complete list of recommendations):

Question 1: What impact do intervention programs have on the extent and frequency of drug injection?

The Committee interpreted this question as asking about the extent to which these interventions affect drug-related HIV risk behavior, including frequency of drug use, injection, and sharing of contaminated equipment.

Drug Treatment

Pharmacotherapies: Strong and consistent evidence from a number of well-designed, randomized controlled trials shows that opioid agonist maintenance treatment—including methadone and buprenorphine—is effective in reducing illicit opioid use and increasing retention of opioid-dependent patients in drug abuse treatment (Mattick et al., 2003a,b; Gowing et al., 2004, 2005). There is also strong evidence that this treatment reduces drug-related HIV risk behavior, including frequency of injecting and sharing of equipment (Gowing et al., 2004, 2005). Given the strong evidence of its effectiveness, opioid agonist maintenance treatment should be made widely available, where feasible. The medication should be provided in sufficiently high doses and for a sufficient duration for therapeutic effects to occur (Sees et al., 2000; Vanichseni et al., 1991; Strain et al., 1993; Faggiano et al., 2003). Programs should be scaled up enough to exert a public health impact, provide adequate public health infrastructure, include a plan for sustainability, and balance strategies to decrease potential diversion of treatment drugs with strategies to disseminate them.

Despite strong pharmacological evidence and theoretical potential for naltrexone—an opioid antagonist (see Box S-1)—evidence regarding its efficacy in controlled clinical trials is inconclusive. Efficacy and effectiveness studies of naltrexone treatment have been limited by problems with high patient attrition and the limited patient appeal of naltrexone (Johansson et al., 2006; Minozzi et al., 2006). However, naltrexone may be effective when used in circumstances where patients' adherence to medication and retention in treatment can be closely monitored and facilitated (Cornish et al., 1997; Tennant et al., 1984; Washton et al., 1984; Krupitsky et al., 2004, 2006). Given its potential benefits and lack of harmful effects, naltrexone should be made available, where feasible, as part of a multicomponent drug treatment strategy. However, more research is needed on the effectiveness of naltrexone for various patient populations and settings.

No pharmacotherapies have been found to be consistently efficacious in treating stimulant dependence. More research is urgently needed to identify effective pharmacotherapies for stimulant dependence, particularly for amphetamine-type stimulants, which have emerged as a major problem in many parts of the world.

Psychosocial: While opioid agonist maintenance therapy has been shown to be very effective in treating opioid dependence, no psychosocial intervention alone—without additional pharmacotherapy—has been shown to be efficacious in treating opioid dependence. Research shows that adjunctive psychosocial interventions may improve outcomes for individuals enrolled in opioid agonist treatment (McLellan et al., 1993), but more research is needed on the benefit and cost-effectiveness of adding psychosocial interventions to such treatment in high-risk countries, and the effectiveness of those interventions in particular cultural contexts and patient subgroups. More research is also needed to determine the relative effectiveness of various psychosocial interventions in treating opioid dependence in places where opioid agonist maintenance therapy is not available or accessible.

Because proven pharmacological interventions are available only for opioid addiction and not for stimulants or other classes of injectable drugs, psychosocial approaches are the primary treatment option for individuals dependent on these substances. One such approach—contingency management—entails consistently rewarding patients (with monetary vouchers or other reinforcers) who remain abstinent or fulfill other verifiable treatment objectives, and withholding rewards when patients do not abstain (or successfully accomplish other specified objectives). A number of randomized controlled trials have found that contingency management is associated with longer retention in treatment, and time abstinent from stimulants, among individuals who are primarily dependent on stimulants (Higgins et al., 1991, 1993, 1994, 2000; Petry et al., 2004), and among

individuals who are dependent on both stimulants and opioids and enrolled in agonist maintenance therapy (Piotrowski et al., 1999; Schottenfeld et al., 2005; Peirce et al., 2006). While most studies have examined the efficacy of contingency management for cocaine users, two randomized clinical trials show that it is efficacious in reducing methamphetamine use (Shoptaw et al., 2005, 2006). More research is needed to develop cost-effective and feasible alternatives to voucher-based contingency management for treating stimulant dependence that can be implemented outside research settings.

There is also modest evidence of effectiveness for several additional psychotherapeutic approaches to treating stimulant abuse. These include combined individual drug counseling and intensive group drug counseling, cognitive behavioral therapy, and the community reinforcement approach combined with contingency management (Crits-Christoph et al., 1999; Maude-Griffin et al., 1998; Monti et al., 1997; McKay et al., 1997; Carroll et al., 1994; Higgins et al. 2003; Roozen et al., 2004) (see Chapter 2, Box 2.2 for definitions of these interventions).

There is relatively weak evidence regarding the effectiveness of therapeutic communities, chemical dependency programs, and drug anonymous treatments, but these are an important treatment options for opioid-dependent individuals who will not accept or cannot access opioid agonist maintenance treatment, or for individuals dependent on other classes of drugs (IOM, 1990; Hubbard et al., 2003). Studies have found that length of time in treatment in these programs is the strongest predictor of positive treatment outcomes.

Given the potential benefits and lack of harmful effects, the following treatments should also be made available as part of a multi-component treatment system, where feasible, but should be accompanied by rigorous evaluation: (1) specific behavioral interventions (contingency management, cognitive behavioral therapy, community reinforcement approach, and individual drug counseling for treating stimulant dependence); and (2) chemical dependency treatment, therapeutic communities, and Drug Anonymous groups for patients dependent on any drug class who are interested in abstinence-oriented treatment.

Sterile Needle and Syringe Access

Multi-component programs that include needle and syringe exchange: A large number of studies and review papers—most from developed countries—show that participation in multi-component HIV prevention programs that include NSE is associated with a reduction in drug-related HIV risk behavior, including self-reported sharing of needles and syringes, unsafe injection and disposal practices, and frequency of injection. Al-

though many of the studies have design limitations, this finding is consistent across a large number of studies.

One concern that has been raised is whether HIV prevention programs that include needle and syringe exchange leads to unintended consequences. The few studies that have examined the unintended consequences of programs that include NSE found no evidence that they lead to more new drug users, more frequent injection among established users, expanded networks of high-risk users, changes in crime trends, or more discarded needles in the community. However, few studies have specifically focused on these outcomes, and this issue could benefit from further study.

Given consistent evidence that multi-component HIV prevention programs that include sterile needle and syringe is associated with reductions in drug-related HIV risk behavior, such programs should be implemented where feasible.

Alternative access to needles and syringes: Eliminating criminal penalties for possessing needles and syringes—and enhancing legal access via pharmacy sales, voucher schemes, and physician prescription programs—are alternative avenues for making sterile needles and syringes available to IDUs. Evaluations of these strategies have primarily been conducted in the United States and have focused on the acceptability of such programs by drug users, pharmacists, and physicians. A few studies have examined the impact on drug-related HIV risk behavior, and found suggestive evidence of a reduction. Evidence regarding supervised injecting facilities and vending machines—while encouraging—is insufficient for drawing conclusions on their effectiveness in reducing drug-related HIV risk among IDUs.

Outreach and Education

Several studies and reviews from the developed world—most with weak designs—show a degree of consistency in finding that outreach reduces self-reported drug-related risk behavior. A review by Coyle et al. (1998) included studies that consistently reported that after an outreach intervention, significant declines occurred in self-reported injection drug use (10 of 11 studies), injection frequency (17 of 18 studies), reuse of needles and syringes (16 of 20 studies), and reuse of other equipment such as cookers, cotton, and rinse water (8 of 12 studies). A later review article by Needle and colleagues (2005) updated the 1998 review and confirmed findings that outreach results in self-reported reduction in HIV-related risk behavior. Outreach services should be made available to provide education on risk reduction and links to sterile needle and syringe access programs, drug treatment, and medical and social services for hard to-reach IDUs.

Question 2: What evidence is there on the extent to which these prevention strategies help reduce HIV transmission from IDUs to their sex partners, and through maternal-to-child transmission to their offspring?

Sexual Transmission

Because the primary objective of drug treatment is to reduce or stop drug use, and the goal of sterile needle and syringe access is to reduce exposure to bloodborne infections through contaminated injecting equipment, one would not necessarily expect to see an effect of these interventions on sex-related HIV risk behavior, unless they are combined with additional risk reduction efforts targeting sexual behavior. And indeed, evidence of such an impact is lacking.

Drug Treatment

Evidence from observational studies is weak and inconclusive on whether opioid agonist therapy alone is associated with reductions in high-risk sexual behavior (Gowing et al., 2004, 2005). Some studies suggest that methadone maintenance therapy is associated with small reductions—compared with pretreatment baseline measures—in the number of sexual partners and exchanges of sex for money or drugs, but that it has virtually no effect on reported rates of unprotected sex (Gowing et al., 2004, 2005). One study assessed the impact of naltrexone on self-reported high-risk sex behavior (Krupitsky et al., 2006). While patients who remained in treatment reported declines in high-risk sex behavior, none of the changes were statistically significant. Some evidence shows that targeted psychosocial interventions are effective in reducing sex-related HIV risk behavior among stimulant-dependent individuals (Prendergast et al., 2001; Gibson et al., 1998; Shoptaw et al., 2005). Efforts should be made to combine effective programs that address sex-related HIV risk behavior with drug treatment programs.

Sterile Needle and Syringe Access Programs

Few studies have evaluated the effect of NSEs on sex-related HIV risk behavior. In two early prospective cohort studies, participants in needle and syringe exchange reported decreases in sex-related risk behavior (Donoghoe, 1989; Hart, 1989). However, this issue has not been well studied, and the existing evidence is insufficient to determine the effectiveness of NSE in reducing sex-related risk. Sterile needle and syringe access programs should focus additional efforts on reducing sex-related HIV risk behavior.

Outreach and Education

There is limited evidence that outreach influences self-reported sex-related risk. A review by Coyle et al. (1998) found that 16 of 17 studies showed an increase in self-reported condom use, or a decrease in self-reported unprotected sex, after outreach. The review authors note, however, that a large percentage of IDUs continued to practice high-risk sexual behavior. A review by Needle et al. (2005) showed that outreach can increase condom use, but found smaller reductions in sex-related HIV risk behavior than in drug-related HIV risk behavior.

A meta-analysis by Semaan et al. (2002) showed that some interventions have lowered sexual risk among IDUs, including outreach based on multiple theories and strategies, peer interventions, and skills training. A study of network-oriented peer outreach suggests that interventions that focus on social roles and identity can reduce injection risk behavior and increase condom use with casual sex partners (Latkin et al., 2003).

Outreach and education programs should focus more on reduction of sex-related HIV risk behavior.

Perinatal Transmission

Perinatal transmission from HIV-infected female IDUs and infected female sex partners of IDUs to their children is a growing concern. The magnitude of IDU-associated perinatal transmission has not been systematically examined, but some studies suggest that it is a major problem. For example, according to one report, most HIV-infected infants born in the Russian Federation between 1996 and 2001 apparently had mothers who were either IDUs or sexual partners of IDUs (UNODC, 2005). The risk of mother-to-child transmission can be greatly reduced by providing antiretroviral drugs to women during pregnancy and labor, and to infants during the first weeks of life (WHO, 2004b). The World Health Organization provides recommendations on using antiretroviral therapy to prevent mother-to-child transmission (WHO, 2004b).

Question 3: How effective are drug treatment programs, sterile needle and syringe access programs, and outreach in reducing HIV transmission among IDUs?

Drug Treatment

Pharmacotherapies: Evidence from prospective cohort and case-control studies shows that continuous opioid agonist maintenance treatment is associated with protection against HIV seroconversion (Moss et al., 1994;

Serpellini and Carrieri, 1994; Williams et al., 1992). These studies also show that the risk of HIV seroconversion is inversely related to the length of time in treatment. However, the possibility of bias in these findings from self-selection cannot be ruled out: that is, patients who resist treatment or engage in risky behaviors may be more likely to leave treatment, while patients who engage in fewer HIV risk behaviors may be more likely to stay in treatment longer. No studies have examined the impact of naltrexone on HIV incidence.

Psychosocial: No studies have examined the impact of individual (i.e., not in conjunction with opioid agonist maintenance treatment) psychosocial interventions for substance abuse treatment on HIV incidence.

Sterile Needle and Syringe Access Programs

Multi-component programs that include needle and syringe exchange: The Committee found that virtually all evaluated programs combined NSE with other prevention strategies, such as outreach, risk reduction education, condom distribution, bleach distribution and education on needle disinfection, and referrals to substance abuse treatment and other health and social services.

Evaluation studies of such multi-component HIV prevention programs have primarily examined their impact on HIV risk behavior rather than HIV incidence. While such studies consistently show that these programs reduce drug-related HIV risk behavior (see the response to Question 1), questions remain about their impact on HIV incidence (Bruneau et al., 1997; Strathdee et al., 1997; Schechter et al., 1999; Patrick et al., 1997).

Although not specifically within its charge, the Committee identified five studies that found that multi-component HIV prevention programs that include NSE have significantly less impact on transmission and acquisition of hepatitis C virus than on HIV (Hagan and Thiede, 2000; Hahn et al., 2001; Sarkar et al., 2003; Taylor et al., 2000; Mansson et al., 2000). This is possibly because NSEs do not always provide other clean equipment (such as cookers and cotton) that, when contaminated, may lead to hepatitis C infection.

While evidence shows that multi-component prevention programs are associated with reductions in drug-related HIV risk behavior, questions remain about the specific contribution of individual elements to reductions in risk behavior and HIV incidence. Elements of these multi-component prevention programs can be resource intensive. Further research is needed to identify the most effective and cost-effective combination of programs that are feasible to implement in high-risk countries. While these questions could be addressed in several ways, one approach would be a trial random-

ized at the community level (community randomized trial) to evaluate the effectiveness and cost-effectiveness of multi-component programs of increasing complexity. Such a trial could specifically assess the impact of needle and syringe exchange and outreach components on the primary outcome measure—incidence of HIV infection (and, as feasible, hepatitis C infection)—as well as important secondary outcome measures (see Appendix E for further details).

Disinfection programs: Laboratory studies show that undiluted bleach can inactivate HIV in injecting equipment, and that undiluted bleach is more efficacious than other tested disinfectants (NRC and IOM, 1995). However, although bleach disinfection works in the laboratory, field studies show that, in practice, drug users do not correctly follow disinfection procedures, and that they fail to disinfect syringes effectively (Carlson et al., 1998; Gleghorn et al., 1994; McCoy et al., 1994). As a result, concerted effort should be made to increase the use of effective procedures for disinfecting shared equipment. IDUs should rely on disinfection to prevent infection with HIV and hepatitis C virus only when they cannot stop injecting or do not have access to new, sterile injecting equipment. While undiluted bleach is the most effective disinfectant, bleach may not be available or acceptable in some settings, and alternative disinfectants may be used or needed.

Outreach and Education

Evidence is very limited regarding the impact of outreach on HIV incidence. The Committee found only one study that directly examined that impact (Wiebel et al., 1996). This study found that HIV seroconversion fell from 8.4 to 2.4 per 100 person-years among IDUs receiving street-based outreach in Chicago from 1988 to 1992 (Wiebel et al., 1996).

Question 4: To what extent do these programs also increase the use of health and social services and drug treatment?

This issue has not been well-studied across interventions. Drug treatment services are not always well integrated with other health and social programs (WHO et al., 2004). Few studies have examined whether participation in drug dependence treatment leads to increases in the use of health and social services. Studies in the United States show that providing basic primary care as part of drug treatment reduces emergency department use and hospitalization among IDUs (Friedmann et al., 2006; Samet et al., 2001). Providing directly administered antiretroviral therapy to HIV-seropositive IDUs can also improve adherence and treatment outcomes

(Lucas et al., 2006; Moatti et al., 2000). However, it is important to monitor potential interactions between antiretroviral medications and opioid agonist maintenance drugs (Iribarne et al., 1998; McCance-Katz et al., 2001; McCance-Katz et al., 2003; McCance-Katz et al., 2006). Studies indicate that IDUs can benefit from integrated drug treatment, HIV care, and other health and social services, but that further research is needed on optimal strategies for linking or coordinating drug dependence treatment with health and social services.

The few studies of multi-component HIV prevention programs that include needle and syringe exchange and link drug users with health and social services showed a moderate uptake of these services (Porter et al., 2002; Riley et al., 2002; Strathdee et al., 1999). However, none of the studies included comparison or control groups, so the overall use of such services among drug users who do not rely on NSE is unknown.

Question 5: What evidence is there that programs aimed at reducing the risk of HIV transmission among IDUs are more effective when they are part of a comprehensive array of services?

While definitions vary, many health policy and research organizations recommend a comprehensive HIV prevention strategy for IDUs. For instance, the World Health Organization (WHO) recommends a comprehensive HIV prevention program for IDUs that includes outreach, information, education, and communication, risk reduction counseling, HIV testing and counseling, disinfection programs, sterile needle and syringe access programs, disposal of used injecting equipment, drug treatment services, agonist pharmacotherapy programs, HIV/AIDS treatment and care, primary health care, and peer education (WHO, 2005b). Similarly, the U.S. National Institute on Drug Abuse (NIDA, 2002) recommends comprehensive programs that encompass three approaches: community-based outreach, drug abuse treatment, and sterile needle and syringe access. These three approaches include a voluntary HIV counseling and testing component and may include many components cited by WHO.

As noted, the Committee found that most prevention programs have multiple components. However, there are few, if any, examples of true "comprehensive" programs. As such, the evidence does not exist to fully answer this question.

CONSIDERATIONS FOR POLICYMAKERS

High-risk countries should act now to prevent the growing problem of HIV infection among IDUs, their partners, and children. The design of

approaches to respond to the HIV epidemic among injecting drug users depends on many factors. Scientific evidence should provide the foundation of the policymaking process. However, any programmatic strategy must factor in the local context, and local programs must be tailored to that context.

Economics in resource-constrained countries is one key factor that can influence the choice of programs and the strategy and pace with which they are implemented. Cost-effectiveness and cost-benefit analyses are standard economic techniques used to guide resource allocation decisions. Models and empirical data from the United States and other resource-rich countries show that methadone maintenance treatment is associated with lower expenditures for injection-related events, such as comorbidity, crime, and transmission of HIV infection to others (Gerstein et al., 1997; Pollack and Heimer, 2004). Some recent studies—mostly mathematical models of the costs of HIV transmission among injecting drug users—also suggest that programs that include needle and syringe exchange are cost-effective (e.g., Laufer, 2001; Cabases and Sanchez, 2003). While there is notable evidence that both NSE and methadone maintenance therapy are quite cost-effective in resource-rich countries, these studies are not themselves strong evidence for cost-effectiveness in high-risk countries. Thus, while savings can be similarly anticipated in developing countries, both program costs and the magnitude of these savings will vary by country, establishing the question of cost-effectiveness as an important research topic.

For HIV prevention efforts to exert a public health impact, they need to be scaled up to provide adequate coverage of the target population(s). Scaling up prevention programs imposes certain infrastructure requirements. These include the availability of a sufficient pool of trained treatment providers, pharmacists, outreach workers, drug and alcohol counselors, infectious disease specialists, and other professionals to carry out the chosen programs, as well as the physical infrastructure, commodities, and funding to enable them to do so. In some places, broad scale-up of intervention packages will require a parallel scale-up of training and accreditation programs for health care workers. Similarly, countries creating or expanding pharmacotherapy programs for opioid dependence may need to adopt or enhance clinical guidelines (regarding patient eligibility criteria, dosage levels, and contraindications with other drugs, for example) and regulations. Information systems will be needed to track and ensure a consistent supply of commodities such as medications and needles. Some high-risk countries may have limited public health, drug treatment, and overall medical infrastructure and operating capacity. These countries must make pragmatic decisions regarding which approaches they can realistically pursue.

Public perceptions also help shape the choice of strategies to prevent HIV transmission and reduce illicit drug use. Some view public health

interventions that provide access to sterile injecting equipment or opioid agonist treatment negatively because these interventions aim to reduce the harms related to drug use rather than prevent drug use itself (NRC and IOM, 1995; Gostin, 1991). These groups may see such harm reduction efforts as condoning rather than condemning illegal drug use. Local communities may also object to programs that include needle and syringe exchange and opioid agonist maintenance treatment because they fear that these programs will attract drug users who may commit crimes and discard needles and other drug paraphernalia in their neighborhoods (NRC and IOM, 1995).

Several studies suggest that the involvement and education of key stakeholders, such as community members, government agencies, nongovernmental groups, public health officials, and law enforcement officials are critical to the success of HIV prevention programs for IDUs. Consultation with community leaders before the initiation of needle and syringe exchange in Thailand and Vietnam was key to their success (Gray, 1995; 1998; Quan et al., 1998). A key realization when such communication occurs is that many disagreements over priorities and strategies stem from a lack of information about the focus, methods, and evidence base of the competing factions. A common understanding that each domain wishes to prevent the needless human suffering of an emerging HIV epidemic is essential. The Committee recommends that public health and criminal justice officials, key community leaders (religious, educational), and community members work together at international, national, regional, and local levels to develop interventions that balance their respective missions in fighting both HIV/AIDS and drug epidemics.

Concerted national efforts to limit the transmission of HIV among IDUs must begin now. Nations must approach these efforts with both immediacy, to break the cycle of HIV transmission, but also with a longer-term view, to sustain progress.

Although reviewing the evidence on primary programs for preventing drug use was beyond the scope of its charge, the Committee believes that programs to prevent the initiation of injecting drug use—and drug use in general—can and should be part of a comprehensive, sustained approach to preventing HIV transmission among IDUs. Broader population-based efforts at HIV awareness and prevention can provide a foundation for sustaining such efforts for IDUs.

Similarly, investments in the infrastructure to deliver clinical and supportive services to the general population will be needed and will have benefits beyond the IDU population. Maintaining infrastructure and sustaining funding is central to ensuring continuous services. Programs that do not have sustainable funding are at risk of interruption. Service interruptions could have serious implications for individuals receiving medication

for opioid dependence and other IDUs receiving treatment or preventive services.

As part of a sustained effort, the Committee repeats its recommendation that such approaches be monitored and evaluated, and modified based on such evaluations. Scale-up of prevention efforts should include staggered program designs or other approaches that permit the evaluation of effectiveness, alongside more rigorous efforts to experiment with different implementation choices to see which ones work best.

CONCLUSION

Nations where the HIV pandemic is newly emerging can and should take effective action now to stem the tide of this tragic and preventable illness. In countries where injecting drug use is the primary source of HIV infection, national programs must address the challenges of both drug use and HIV. The Committee has reviewed the evidence regarding interventions for injecting drug use and HIV among IDUs, and hopes it has provided policymakers a knowledge base regarding what works. The Committee recognizes though that each country will pursue a different combination of interventions, reflecting its economic circumstances and legal, ethical, and cultural traditions. However, these policy decisions should not be based on erroneous understanding if scientific truth is available. The Committee believes that the evidence-based conclusions and recommendations in this report can provide an important foundation for governments and communities engaging in economic, legal, and ethical debates about these issues.

Evidence on effective interventions provides a solid basis for action now. The experiences of other nations with extensive HIV epidemics underscore the urgent need for an immediate response. As policy unfolds into programmatic action, nations should also evaluate their implementation, to inform the next generation of responses to drug dependence and HIV.

BOX S-2 Recommendations

Recommendations Regarding Treatment for Drug Dependence (Chapter 2)

Recommendation 2-1: Given the strong evidence of its effectiveness in treating opioid dependence, opioid agonist maintenance treatment should be made widely available where feasible. Such programs should include:

- The necessary infrastructure to make treatment widely available (e.g., clinics, trained health workers) and a strategy to ensure sustainability.
- Assurance of adequate dosage and treatment duration.
- A balance between strategies to decrease diversion of treatment medication and strategies to disseminate the treatment.
- An evaluation component to monitor treatment implementation, quality, and outcomes.
- Monitoring of potential drug interactions between antiretroviral medications and opioid agonist maintenance drugs for HIV-infected IDUs.

Recommendation 2-2: Given the potential benefits and lack of harmful effects, the following treatments should also be made available as part of a multi-component treatment system, where feasible, but should include a rigorous evaluation component:

- Naltrexone treatment for opioid-dependent patients interested in abstinence-oriented treatment.
- Specific behavioral treatments (contingency management, cognitive behavioral therapy, community reinforcement approach, motivational interviewing, and individual drug counseling) for treating stimulant dependence.
- Chemical dependency treatment, therapeutic communities, and Drug Anonymous groups for patients dependent on any drug class who are interested in abstinence-oriented treatment.

Recommendation 2-3: Given the relative weakness of the evidence, further research should occur on the following issues related to treatment for drug dependence:

- The additional benefits and cost-effectiveness of adding psychosocial interventions to opioid agonist maintenance treatment for opioid-dependent people in high-risk countries, and the relative effectiveness of those interventions in particular cultural contexts and for particular patient subgroups.
- Pharmacotherapies for stimulant abuse, particularly amphetamine-type stimulants which have emerged as a major problem in many parts of the world.
- The effectiveness of naltrexone for different patient populations and in different settings.
- The relative effectiveness of various psychosocial interventions in treating opioid dependence in places where opioid agonist maintenance therapy is not available or accessible.
- Developing cost-effective and feasible alternatives to voucher-based contingency management approaches for treating stimulant dependence.
- Effective strategies for reducing sex-related risk behavior of IDUs in treatment.
- Optimal strategies for linking drug dependence treatment with health and social services.

Recommendations Regarding Sterile Needle and Syringe Access and Outreach and Education (Chapter 3)

Recommendation 3-1: Given consistent evidence that multi-component HIV prevention programs that include sterile needle and syringe access reduce drug-related HIV risks, such programs should be implemented where feasible.

Recommendation 3-2: Multi-component HIV prevention programs that include sterile needle and syringe access should:

- Maximize their accessibility to the largest number of IDUs by using multiple access points and methods of delivery.
- Focus on reducing sex-related HIV risk behavior.
- Actively refer IDUs to other services, such as substance abuse treatment, HIV voluntary counseling and testing and, if appropriate, antiretroviral treatment for HIV.
- Focus additional efforts on preventing hepatitis C infection, such as by providing sterile cotton swabs, alcohol wipes for cleaning injection sites, sterile water, cookers, and other disinfection supplies.
- Incorporate strong program and component evaluations, and where feasible, include comparison populations or regions.

Recommendation 3-3: Because field studies have shown that drug users often fail to properly disinfect injecting equipment, concerted effort should be made to increase the uptake of effective procedures for disinfecting shared equipment. IDUs should rely on disinfection to prevent HIV and hepatitis C virus (HCV) infection only when they cannot stop injecting or do not have access to new, sterile injecting equipment.

Recommendation 3-4: Outreach services should be made available to provide education on risk reduction and links to sterile needle and syringe access programs, drug treatment, and medical and social services for hard to-reach IDUs.

Recommendation 3-5: The Committee recommends that additional research focus on:

- The impact of outreach and education and multi-component programs that include sterile needle and syringe access on sexual risk reduction.
- Integration of effective strategies for reducing sexual risk behavior and sexual transmission of HIV into multi-component programs that include sterile needle and syringe exchange and outreach and education.
- The potential unintended consequences of HIV prevention programs that include needle and syringe exchange, such as increases in new drug users or in discarded needles in the community, and strategies to address such problems, if they are found.
- Identifying the simplest, most acceptable effective disinfection techniques using bleach, and the best methods for educating IDUs on these techniques.
- The effectiveness of alternative disinfectants in field settings, particularly in countries where bleach is not available or acceptable.
- Identifying effective strategies for preventing HCV among IDUs.
- The costs and contributions of individual elements of multi-component programs that include needle and syringe exchange on HIV-related risk behavior and HIV incidence.

continued

BOX S-2 Recommendations

Recommendations Regarding Taking Action (Chapter 4)

Recommendation 4-1: Because a variety of interventions have been shown to be effective, high-risk countries should act now to prevent the growing problem of HIV among IDUs, their partners, and children.

Recommendation 4-2: To increase their acceptability and likelihood of success, HIV prevention interventions for IDUs should be:

- Tailored to local circumstances and implemented in a culturally appropriate manner;
- Coupled with cost-effectiveness evaluations to improve resource-allocation decisions;
- Scaled-up to provide adequate coverage of the interventions to the target populations in order for programs to have a public health impact;
- Integrated with strategies to combat stigma and discrimination among drug users and HIV- infected people;
- Coordinated among national, regional, and local public health, criminal justice, and community leaders to develop a framework for interventions that balance their respective missions;
- Complementary to broader interventions in drug use and HIV, including primary prevention;
- Built upon plans for fiscal and infrastructure sustainability;
- Coupled with monitoring and evaluation.

REFERENCES

Aceijas C, Stimson GV, Hickman M, Rhodes T. 2004. Global overview of injecting drug use and HIV infection among injecting drug users. *AIDS*. 18(17):2295–2303.

Bruneau J, Lamothe F, Franco E, Lachance N, Desy M, Soto J, Vincelette J. 1997. High rates of HIV infection among injection drug users participating in needle exchange programs in Montreal: Results of a cohort study. *American Journal of Epidemiology*. 146(12):994–1002.

Burris S, Blankenship KM, Donoghoe M, Sherman S, Vernick JS, Case P, Lazzarini Z, Koester S. 2004. Addressing the "risk environment" for injection drug users: The mysterious case of the missing cop. *Milbank Quarterly*. 82(1):125–156.

Cabases J, Sanchez E. 2003. Costs and effectiveness of a syringe distribution and needle exchange program for HIV prevention in a regional setting. *The European Journal of Health Economics*. 4(3):203–208.

Carlson RG, Wang J, Siegal HA, Falck RS. 1998. A preliminary evaluation of a modified needle-cleaning intervention using bleach among injection drug users. *AIDS Education and Prevention*. 10(6):523–532.

Carroll KM, Rounsaville BJ, Gordon LT, Nich C, Jatlow PM, Bisighini RM, Gawin FH. 1994. Psychotherapy and pharmacotherapy for ambulatory cocaine abusers. *Archives of General Psychiatry*. 51(12):989–997.

Cornish JW, Metzger D, Woody GE, Wilson D, McLellan AT, Vandergrift B, O'Brien CP. 1997. Naltrexone pharmacotherapy for opioid dependent federal probationers. *Journal of Substance Abuse Treatment*. 14(6):529–534.

Coyle SL, Needle RH, Normand J. 1998. Outreach-based HIV prevention for injecting drug users: A review of published outcome data. *Public Health Reports*. 113(Suppl 1):19–30.

Crits-Christoph P, Siqueland L, Blaine J, Frank A, Luborsky L, Onken LS, Muenz LR, Thase ME, Weiss RD, Gastfriend DR, Woody GE, Barber JP, Butler SF, Daley D, Salloum I, Biship S, Najavits LM, Lis J, Mercer D, Griffin ML, Moras K, Beck AT. 1999. Psychosocial treatments for cocaine dependence. *Archives of General Psychiatry*. 56:493–502.

DHHS (U.S. Department of Health and Human Services). 2006. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. [Online]. Available: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf [accessed August 3, 2006].

Donoghoe MC, Stimson GV, Dolan KA. 1989. Sexual behaviour of injecting drug users and associated risks of HIV infection for non-injecting sexual partners. *AIDS Care*. 1(1): 51–58.

Dunbar JL, Turncliff RZ, Dong Q, Silverman BL, Ehrich EW, Lasseter KC. 2006. Single- and multiple-dose pharmacokinetics of long-acting injectable naltrexone. *Alcoholism, Experimental and Clinical Research*. 30(3):480–490.

Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. 2003. Methadone maintenance at different dosages for opioid dependence. *The Cochrane Database of Systematic Reviews*. (3):CD002208.

Friedmann PD, Hendrickson JC, Gerstein DR, Zhang Z, Stein MD. 2006. Do mechanisms that link addiction treatment patients to primary care influence subsequent utilization of emergency and hospital care? *Medical Care*. 44(1):8–15.

Gerstein DR, Johnson RA, Larison CL. 1997. *Alcohol and Other Drug Treatment for Parents and Welfare Recipients: Outcomes, Costs, and Benefits*. Washington, DC: U.S. Department of Health and Human Services.

Gibson DR, McCusker J, Chesney M. 1998. Effectiveness of psychosocial interventions in preventing HIV risk behaviour in injecting drug users. *AIDS*. 12(8):919–929.

Gleghorn AA, Doherty MC, Vlahov D, Celentano D, Jones T. 1994. Inadequate bleach contact times during syringe cleaning among injection drug users. *Journal of Acquired Immune Deficiency Syndromes*. 7(7):767–772.

Gostin L. 1991. An alternative public health vision for a national drug strategy: "Treatment works." *Houston Law Review*. 28(1):285–308.

Gowing LR, Farrell M, Bornemann R, Ali R. 2004. Substitution treatment of injecting opioid users for prevention of HIV infection. *The Cochrane Database of Systematic Reviews*. (4):CD004145.

Gowing LR, Farrell M, Bornemann R, Sullivan LE, Ali RL. 2005. Brief report: Methadone treatment of injecting opioid users for prevention of HIV infection. *Journal of General Internal Medicine*. 20:1–3.

Gray J. 1995. Operating needle exchange programmes in the hills of Thailand. *AIDS Care*. 7(4):489–499.

Gray J. 1998. Harm reduction in the hills of northern Thailand. *Substance Use and Misuse*. 33(5):1075–1091.

Hagan H, Thiede H. 2000. Changes in injection risk behavior associated with participation in the Seattle needle-exchange program. *Journal of Urban Health*. 77(3):369–382.

Hahn JA, Page-Shafer K, Lum PJ, Ochoa K, Moss AR. 2001. Hepatitis C virus infection and needle exchange use among young injection drug users in San Francisco. *Hepatology*. 34(1):180–187.

Hart GJ, Carvell AL, Woodward N, Johnson AM, Williams P, Parry JV. 1989. Evaluation of needle exchange in central London: Behaviour change and anti-HIV status over one year. *AIDS*. 3(5):261–265.

Higgins ST, Budney AJ, Bickel WK, Hughes JR, Foerg F, Fenwick W. 1991. A behavioral approach to achieving initial cocaine abstinence. *American Journal of Psychiatry*. 148:1218–1224.

Higgins ST, Budney AJ, Bickel WK, Hughes JR, Foerg F, Badger G. 1993. Achieving cocaine abstinence with a behavioral approach. *American Journal of Psychiatry*. 150:763–769.

Higgins ST, Budney AJ, Bickel WK, Foerg FE, Donham R, Badger GJ. 1994. Incentives improve outcome in outpatient behavioral treatment of cocaine dependence. *Archives of General Psychiatry*. 51:568–576.

Higgins ST, Wong CJ, Badger GJ, Ogden DE, Dantona RL. 2000. Contingent reinforcement increases cocaine abstinence during outpatient treatment and 1 year of follow-up. *Journal of Consulting and Clinical Psychology*. 68:64–72.

Higgins ST, Sigmon SC, Wong CJ, Heil SH, Badger GJ, Donham R, Dantona RL, Anthony S. 2003. Community reinforcement therapy for cocaine dependent outpatients. *Archives of General Psychiatry*. 60(10):1043–1052.

Hubbard RL, Craddock SG, Anderson J. 2003. Overview of 5-year follow-up outcomes in the drug abuse treatment outcome studies (DATOS). *Journal of Substance Abuse Treatment*. 25:125–134.

IOM (Institute of Medicine). 1990. *Treating Drug Problems: Volume 1*. Washington, DC: National Academy Press.

IOM. 1995. *Federal Regulation of Methadone Treatment*. Washington, DC: National Academy Press.

IOM. 1997. *Dispelling the Myths About Addiction*. Washington, DC: National Academy Press.

Iribarne C, Berthou F, Carlhant D, Dreano Y, Picart D, Lohezic F, Riche C. 1998. Inhibition of methadone and buprenorphine N-dealkylations by three HIV-1 protease inhibitors. *Drug Metabolism and Disposition*. 26(3):257–260.

Johannson BA, Berglund M, Lindgren A. 2006. Efficacy of maintenance treatment with naltrexone for opioid dependence: A meta-analytical review. *Addiction*. 101:491–503.

Krupitsky EM, Zvartau EE, Masalov DV, Tsoi MV, Burakov AM, Egorova VY, Didenko TY, Romanova TN, Ivanova EB, Bespalov AY, Verbitskaya EV, Naznanov NG, Grinenko AY, O'Brien CP, Woody GE. 2004. Naltrexone for heroin dependence treatment in St. Petersburg, Russia. *Journal of Substance Abuse Treatment*. 26(4):285–294.

Krupitsky EM, Zvartau EE, Masalov DV, Tsoy MV, Burakov AM, Egorova VY, Didenko TY, Romanova TN, Ivanova EB, Bespalov AY, Verbitskaya EV, Neznanov NG, Grinenko AY, O'Brien CP, Woody GE. 2006. Naltrexone with or without fluoxetine for preventing relapse to heroin addiction in St. Petersburg, Russia. *Journal of Substance Abuse Treatment*. In press, corrected proof. [Available online July 24, 2006].

Latkin C, Sherman S, Knowlton A. 2003. HIV prevention among drug users: Outcome of a network-orientated peer outreach intervention. *Health Psychology*. 22(4):332–339.

Laufer FN. 2001. Cost-effectiveness of syringe exchange as an HIV prevention strategy. *Journal of Acquired Immune Deficiency Syndromes*. 28(3):273–278.

Lucas GM, Mullen BA, Weidle PJ, Hader S, MCaul ME, Moore RD. 2006. Directly administered antiretroviral therapy in methadone clinics is associated with improved HIV treatment outcomes, compared with outcomes among concurrent comparison groups. *Clinical Infectious Diseases*. 42:1628–1635.

MacCoun R, Reuter P. 2001. *Drug War Heresies: Learning from Other Vices, Times, and Places*. Cambridge, UK: Cambridge University Press.

Mansson AS, Moestrup T, Nordenfelt E, Widell A. 2000. Continued transmission of hepatitis B and C viruses, but no transmission of human immunodeficiency virus among intravenous drug users participating in a syringe/needle exchange program. *Scandinavian Journal of Infectious Diseases*. 32(3):253–258.

Mattick RP, Breen C, Kimber J, Davoli M. 2003a. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *The Cochrane Database of Systematic Reviews*. (2):CD002209.

Mattick RP, Kimber J, Davoli M. 2003b. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *The Cochrane Database of Systematic Reviews*. (2):CD002207.

Maude-Griffin PM, Hohenstein JM, Humfleet GL, Reilly PM, Tusel DJ, Hall SM. 1998. Superior efficacy of cognitive-behavioral therapy for crack cocaine abusers: Main and matching effects. *Journal of Consulting and Clinical Psychology*. 66:832–837.

Mayet S, Farrell M, Ferri M, Amato L, Davoli M. 2004. Psychosocial treatment for opiate abuse and dependence. *Cochrane Database of Systematic Reviews*. (4):CD004330.

McCance-Katz EF, Rainey PM, Friedland G, Kosten TR, Jatlow P. 2001. Effect of opioid dependence pharmacotherapies on zidovudine disposition. *American Journal of Addictions*. 10(4):296–307.

McCance-Katz EF, Rainey PM, Friedland G, Jatlow P. 2003. The protease inhibitor lopinavir-ritonavir may produce opiate withdrawal in methadone-maintained patients. *Clinical Infectious Diseases*. 37(4):476–482.

McCance-Katz EF, Rainey PM, Smith P, Morse GD, Friedland G, Boyarsky B, Gourevitch M, Jatlow P. 2006. Drug interactions between opioids and antiretroviral medications: Interaction between methadone, LAAM, and delavirdine. *American Journal on Addictions*. 15(1):23–34.

McCoy CB, Rivers JE, McCoy HV, Shapshak P, Weatherby NL, Chitwood DD, Page JB, Inciardi JA, McBride DC. 1994. Compliance to bleach disinfection protocols among injecting drug users in Miami. *Journal of Acquired Immune Deficiency Syndromes*. 7(7):773–776.

McKay JR, Alterman AI, Cacciola JS, Rutherford MJ, O'Brien CP, Koppenhaver J. 1997. Group counseling versus individualized relapse prevention aftercare following intensive outpatient treatment for cocaine dependence. *Journal of Consulting and Clinical Psychology*. 65:778–788.

McLellan AT, Arndt IO, Metzger DS, Woody GE, O'Brien CP. 1993. The effects of psychosocial services in substance abuse treatment. *Journal of the American Medical Association*. 269(15):1953–1959.

McLellan T, Lewis D, O'Brien C, Kleber H. 2000. Drug dependence, a chronic mental illness: Implications for treatment, insurance, and outcomes evaluation. *Journal of the American Medical Association*. 284(13):1689–1695.

Minozzi S, Amato L, Vecchi S, Davoi M, Kirchmayer U, Verster A. 2006. Oral naltrexone maintenance treatment for opioid dependence. *The Cochrane Database of Systematic Reviews*. (1):CD001333.

Moatti JP, Carrieri MP, Spire B, Gastaut JA, Cassuto JP, Moreau J, Manif 2000 study group. 2000. Adherence to HAART in French HIV-infected injecting drugs users: The contribution of buprenorphine drug maintenance treatment. *AIDS*. 14(2):151–155.

Monti PM, Rohsenow DJ, Michalec E, Martin RA, Abrams DB. 1997. Brief coping skills treatment for cocaine abuse: Substance abuse outcomes at three months. *Addiction*. 92:1717–1728.

Moss AR, Vranizan K, Gorter R, Bacchetti P, Watters J, Osmond D. 1994. HIV seroconversion in intravenous drug users in San Francisco, 1985-1990. *AIDS*. 8(2): 223–231.

Needle RH, Burrows D, Friedman SR, Dorabjee J, Touze G, Badrieva L, Grund J-PC, Kumar MS, Nigro L, Manning G, Latkin C. 2005. Effectiveness of community-based outreach in preventing HIV/AIDS among injecting drug users. *International Journal of Drug Policy*. 16(Suppl 1):S45–S57.

NIDA (National Institute on Drug Abuse). 2002. *Principles of HIV Prevention in Drug-Using Populations: A Research-Based Guide*. Washington, DC: NIDA. [Online]. Available: http://www.nida.nih.gov/POHP/FAQ_1.html [accessed June 22, 2006].

NRC (National Research Council) and IOM (Institute of Medicine). 1995. *Preventing HIV Transmission: The Role of Sterile Needles and Bleach*. Washington, DC: National Academy Press.

O'Brien C, Kampman K. 2004. Opioids: Antagonists and partial agonists. In: *The American Psychiatric Association Textbook of Substance Abuse Treatment*. 3rd edition. Washington, DC: American Psychiatric Press, Inc. Pp. 305–319.

Patrick DM, Strathdee SA, Archibald CP, Ofner M, Craib KJ, Cornelisse PG, Schechter MT, Rekart ML, O'Shaughnessy MV. 1997. Determinants of HIV seroconversion in injection drug users during a period of rising prevalence in Vancouver. *International Journal of STDs and AIDS*. 8(7):437–445.

Peirce JM, Petry NM, Stitzer ML, Blaine J, Kellogg S, Satterfield F, Schwartz M, Krasnansky J, Pencer E, Silva-Vazquez L, Kirby KC, Royer-Malvestuto C, Roll JM, Cohen A, Copersino ML, Kolodner K, Li R. 2006. Effects of lower-cost incentives on stimulant abstinence in methadone maintenance treatment: A national drug abuse treatment clinical trials network study. *Archives of General Psychiatry*. 63(2):201–208.

Petry NM, Tedford J, Austin M, Nich C, Carroll KM, Rounsaville BJ. 2004. Prize reinforcement contingency management for treating cocaine users: How low can we go, and with whom? *Addiction*. 99:349–360.

Piotrowski NA, Tusel DJ, Sees KL, Reilly PM, Banys P, Meek P, Hall SM. 1999. Contingency contracting with monetary reinforcers for abstinence from multiple drugs in a methadone program. *Experimental and Clinical Psychopharmacology*. 7(4):399–411.

Pollack H, Heimer R. 2004. Impact and cost-effectiveness of methadone maintenance programs for HIV and hepatitis C prevention. In: Jager J, Limburg W, Kretzschmar M, Postma M, Wiessing L, eds. *Hepatitis C and Injecting Drug Use: Impact, Costs, and Policy Options*. Lisbon: European Monitoring Centre for Drugs and Drug Addiction. 7:345–371.

Porter J, Metzger D, Scotti R. 2002. Bridge to services: Drug injectors' awareness and utilization of drug user treatment and social service referrals, medical care, and HIV testing provided by needle exchange programs. *Substance Use and Misuse*. 37(11):1305–1330.

Prendergast ML, Urada D, Podus D. 2001. Meta-analysis of HIV risk reduction interventions with drug abuse treatment programs. *Journal of Consulting and Clinical Psychology*. 69(3):389–405.

Quan VM, Chung A, Abdul-Quader AS. 1998. The feasibility of a syringe-needle exchange program in Vietnam. *Substance Use and Misuse*. 33(5):1055–1067.

Riley ED, Wu AW, Junge B, Marx M, Strathdee SA, Vlahov D. 2002. Health services utilization by injection drug users participating in a needle exchange program. *American Journal of Drug and Alcohol Abuse*. 28(3):497–511.

Rhodes T, Singer M, Bourgois P, Friedman SR, Strathdee SA. 2005. The social structural production of HIV risk among injecting drug users. *Social Science Medicine*. 61(5):1026–1044.

Roozen HG, Boulogne JJ, van Tulder MW, van den Brink W, De Jong CAJ, Kerkhof AJFM. 2004. A systematic review of the effectiveness of the community reinforcement approach in alcohol, cocaine and opioid addiction. *Drug and Alcohol Dependence*. 74:1–13.

Samet JH, Friedmann P, Saitz R. 2001. Benefits of linking primary medical care and substance abuse services: Patient, provider, and societal perspectives. *Archives of Internal Medicine*. 161:85–91.

Sarkar K, Mitra S, Bal B, Chakraborty S, Bhattacharya SK. 2003. Rapid spread of hepatitis C and needle exchange programme in Kolkata, India. *Lancet*. 361(9365):1301–1302.

Schechter MT, Strathdee SA, Cornelisse PG, Currie S, Patrick DM, Rekart ML, O'Shaughnessy MV. 1999. Do needle exchange programmes increase the spread of HIV among injection drug users?: An investigation of the Vancouver outbreak. *AIDS*. 13(6):F45–F51.

Schottenfeld RS, Chawarski MC, Pakes JR, Pantalon MV, Carroll KM, Kosten TR. 2005. Methadone versus buprenorphine with contingency management or performance feedback for cocaine and opioid dependence. *American Journal of Psychiatry*. 162(2): 340–349.

Sees KL, Delucchi KL, Masson C, Rosen A, Clark HW, Robillard H, Banys P, Hall SM. 2000. Methadone maintenance versus 180-day psychosocially enriched detoxification for treatment of opioid dependence: A randomized controlled trial. *Journal of the American Medical Association*. 283(10):1303–1310.

Semaan S, Des Jarlais DC, Sogolow E, Johnson WD, Hedges LV, Ramirez G, Flores SA, Norman L , Sweat MD, Needle R. 2002. A meta-analysis of the effect of HIV prevention interventions on the sex behaviors of drug users in the United States. *Journal of Acquired Immune Deficiency Syndromes*. 30(Suppl 1):S73–S93.

Serpellini G, Carrieri MP. 1994. Methadone treatment as a determinant of HIV risk reduction among injecting drug users: A nested case-control study. *AIDS Care*. 6(2):215–220.

Shoptaw S, Reback CJ, Peck JA, Yang Xiaowei, Rotheram-Fuller E, Larkins S, Veniegas RC, Freese TE, Hucks-Ortiz C. 2005. Behavioral treatment approaches for methamphetamine dependence and HIV-related sexual risk behaviors among urban gay and bisexual men. *Drug and Alcohol Dependence*. 78:125–134.

Shoptaw S, Huber A, Peck J, Yang X, Liu J, Dang J, Roll J, Shapiro B, Rotheram-Fuller E, Ling W. 2006. Randomized, placebo-controlled trial of sertraline and contingency management for the treatment of methamphetamine dependence. *Drug and Alcohol Dependence*. [Epub available online April 18, 2006].

Strain EC et al. 1993. Dose-response effects of methadone in the treatment of opioid dependence. *Annals of Internal Medicine*. 119:23–27.

Strathdee SA, Patrick DM, Currie SL, Cornelisse PG, Rekart ML, Montaner JS, Schechter MT, O'Shaughnessy MV. 1997. Needle exchange is not enough: Lessons from the Vancouver injecting drug use study. *AIDS*. 11(8):F59–F65.

Strathdee SA, Celentano DD, Shah N, Lyles C, Stambolis VA, Macalino G, Nelson K, Vlahov D. 1999. Needle-exchange attendance and health care utilization promote entry into detoxification. *Journal of Urban Health*. 76(4):448–460.

Taylor A, Goldberg D, Hutchinson S, Cameron S, Gore SM, McMenamin J, Green S, Pithie A, Fox R. 2000. Prevalence of hepatitis C virus infection among injecting drug users in Glasgow 1990-1996: Are current harm reduction strategies working? *Journal of Infectious Diseases*. 40(2):176–183.

Tennant FS, Rawson RA, Cohen AJ, Mann A. 1984. Clinical experience with naltrexone in suburban opioid addicts. *Journal of Clinical Psychiatry*. 45(9 pt 2):42–45.

UNAIDS (Joint United Nations Programme on HIV/AIDS). 2006. *2006 Report on the Global AIDS Epidemic: A UNAIDS 10th Anniversary Special Edition*. Geneva, Switzerland: UNAIDS.

UNODC (United Nations Office on Drugs and Crime). 2005. *2005 World Drug Report*. Vienna, Austria: UNODC.

Vanichseni S, Wongsuwan B, Choopanya K, Wongpanich K. 1991. A controlled trial of methadone maintenance in a population of intravenous drug users in Bangkok: Implications for prevention of HIV. *The International Journal of Addictions*. 26(12):1313–1320.

Washton AM, Pottash AC, Gold MS. 1984. Naltrexone in addicted business executives and physicians. *Journal of Clinical Psychiatry*. 45(9 pt 2):39–41.

WHO (World Health Organization). 2004a. *Evidence for Action: Effectiveness of Community-Based Outreach in Preventing HIV/AIDS Among Injecting Drug Users*. Geneva, Switzerland: WHO.

WHO. 2004b. *Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants: Guidelines on Care, Treatment and Support for Women Living with Hiv/Aids and Their Children in Resource-Constrained Settings*. Geneva, Switzerland: WHO.

WHO. 2005a. *Evidence for Action: Effectiveness of Drug Dependence Treatment in Preventing HIV Among Injecting Drug Users*. Geneva, Switzerland: WHO.

WHO. 2005b. *Policy and Programming Guide for HIV/AIDS Prevention and Care Among Injecting Drug Users*. Geneva, Switzerland: WHO.

WHO. 2005c. *WHO Model List of Essential Medicine*. 14th edition. [Online]. Available: http://whqlibdoc.who.int/hq/2005/a87017_eng.pdf [accessed August 11, 2006].

WHO, UNODC, UNAIDS. 2004. *Substitution Maintenance Therapy in the Management of Opioid Dependence and HIV/AIDS Prevention: Position Paper*. Geneva, Switzerland: WHO.

Wiebel WW, Jimenez A, Johnson W, Ouellet L, Jovanovic B, Lampinen T, Murray J, O'Brien MU. 1996. Risk behavior and HIV seroincidence among out-of-treatment injection drug users: A four-year prospective study. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*. 12(3):282–289.

Williams AB, McNelly EA, Williams AE, D'Aquila RT. 1992. Methadone maintenance treatment and HIV type 1 seroconversion among injecting drug users. *AIDS Care*. 4(1): 35–41.

Introduction

Drug dependence is a complex, chronic, relapsing condition that is often accompanied by severe health, psychological, economic, legal, and social consequences (IOM, 1990, 1995). It is manifested by a complex set of behaviors including compulsive drug craving, seeking, and use that interferes with an individual's physical, mental, and social functioning (IOM, 1997; McLellan et al., 2000). Similar to other chronic conditions, such as heart disease or diabetes, individuals with drug dependence can stabilize their condition by making behavioral changes and with the use of appropriate medications (WHO et al., 2004). Drug-dependent individuals have high rates of medical and psychiatric comorbidity and increased risk of premature mortality (DHHS, 2006). Injecting drug users are particularly vulnerable to HIV and other bloodborne infections (such as hepatitis C) as a result of sharing contaminated injecting equipment. All drug-dependent individuals, including injecting drug users (IDUs), may be at increased risk of HIV infection because of high-risk sexual behaviors.

There are an estimated 13.2 million injecting drug users (IDUs) worldwide—78 percent of whom live in developing or transitional countries (Aceijas et al., 2004). The sharing of contaminated injecting equipment[1] has become a major driving force of the global AIDS epidemic and is the primary mode of HIV transmission in many countries throughout Eastern

[1]Injecting equipment may include needles, syringes, cookers, cotton, and water.

Europe, the Commonwealth of Independent States,[2] and significant parts of Asia (UNAIDS, 2006). In some cases, epidemics initially fueled by the sharing of contaminated injecting equipment are spreading through sexual transmission from IDUs to non-injecting populations, and through perinatal transmission to newborns. Reversing the rise of HIV infections among IDUs has thus become an urgent global public health challenge—one that remains largely unmet.

STUDY GOALS AND APPROACH

In response to this challenge, in 2005 the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the Bill & Melinda Gates Foundation commissioned the Institute of Medicine to undertake an expedited review of the scientific evidence on the effectiveness of strategies to prevent HIV transmission through contaminated injecting equipment, with a specific focus on countries throughout Eastern Europe, the Commonwealth of Independent States, and significant parts of Asia, where injecting drug use is a primary driver of the HIV/AIDS epidemic. In this report, such countries are labeled as "high-risk," indicating that injecting drug use is, or is on the verge of becoming, the primary driver of the HIV epidemic.

The charge to the Committee included five questions. They are listed here in the order in which they are addressed in the chapters. The Committee found it most helpful to first discuss the evidence on the intermediate outcomes of drug-related risk (question one) and sex-related risk (question two) prior to examining the impact on HIV transmission (question three).

1. What impact do needle and syringe exchange, disinfection programs, drug substitution programs, drug treatment programs, and counseling and education have on the extent and frequency of drug injection?
2. What evidence is there on the extent to which these prevention strategies help reduce HIV transmission from IDUs to their sex partners and through maternal-to-child transmission to their offspring?
3. How effective are such programs in reducing HIV transmission among IDUs?
4. To what extent do such programs also increase the use of health and social services and drug treatment?
5. What evidence is there that programs aimed at reducing the risk of HIV transmission among IDUs are more effective when they are part of a

[2]The Commonwealth of Independent States includes Azerbaijan, Armenia, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Russia, Tajikistan, Turkmenistan, Uzbekistan, and Ukraine.

comprehensive array of services, which include outreach, HIV prevention education, counseling, referral to drug substitution treatment, drug rehabilitation services, and medical and psychosocial support?

In response to this charge, the Committee convened a public workshop in Geneva in December 2005 to gather information from experts on IDU-driven HIV epidemics in the most affected regions of the world, including Eastern Europe, the Commonwealth of Independent States, and significant parts of Asia. Experts from other regions also provided information on their experiences in preventing HIV infection among IDUs (see Appendix A for the agenda of this meeting).

The Committee further conducted a comprehensive search of the English language peer-reviewed scientific literature, and evaluated previous systematic reviews and reports on these issues (see Appendix B for an overview of the Committee's literature searches and review methods). While the Committee sought evidence from high-risk countries, the literature review and evaluation included evidence from all over the world. In reviewing the evidence, the Committee grouped the range of HIV prevention strategies for IDUs it was asked to address in the charge into three categories: (1) drug dependence treatment programs, which include both pharmacotherapies and psychosocial interventions; (2) sterile needle and syringe access programs; and (3) outreach and education programs (see Chapter 1 for descriptions of these interventions). The Committee then assessed the evidence it had gathered at a closed meeting in Washington, DC, in March 2006, and during later conference calls.

This report focuses on programs that are designed to prevent the transmission of HIV among injecting drug users. These programs range from efforts to curtail non-medical drug use to those that encourage reduction in high-risk behavior among drug users. The term "harm reduction" is often used to describe programs such as sterile needle and syringe access because their primary aim is to reduce the harms related to drug use among those who are unable or unwilling to stop using drugs. However, because the term has a wide range of interpretations, the Committee refers to all interventions in this report as HIV prevention programs for IDUs.

Several issues are beyond the Committee's charge and are not addressed in this report. First, the committee did not evaluate various drug control policies, such as supply and demand reduction strategies. While a large number of drug users interface with the criminal justice system, the committee did not evaluate the impact of criminal justice programs on drug use, HIV risk behaviors, or HIV transmission. An evaluation of programs such as mandatory drug treatment or diversion of drug users from the criminal justice system into treatment settings was also outside the scope of this study. Similarly, the committee did not evaluate interventions

for primary prevention of drug use, although it believes such approaches are an important complement to strategies to prevent HIV infection among drug users. In addition, the committee did not examine strategies to prevent non-injecting drug users from becoming IDUs.

There are a variety of HIV prevention and treatment programs which, although they apply to IDUs, are not specific to this population. These interventions, such as voluntary counseling and testing, antiretroviral therapy, and prevention and treatment of sexually transmitted infections, target broader populations. While there is a large body of evidence evaluating the effectiveness and efficacy of these interventions, the Committee's review was limited to those interventions specific to IDUs. Therefore, only a brief overview of these broader interventions is presented in Chapter 1.

Certain interventions that specifically target drug-related risk behavior, such as sterile needle and syringe access programs or medications for opioid dependence, would not be expected to decrease sex-related risk behavior, unless sexual risk reduction education or provision of condoms were a component of the program—a fact that studies do not generally reveal. Many communities attempting to address injecting drug use have independent programs to educate the broader population about HIV, reduce high-risk sexual exposures, and enhance condom use for various high-risk populations. While the Committee considered the impact of the specific HIV prevention programs for IDUs that were included in its charge on sex-related risk behavior, an evaluation of the applicability and effectiveness on IDUs of sex-related risk reduction programs at the population level not specifically focused on IDUs was beyond the scope of this report.

Because this report focuses on HIV prevention, it considers but does not fully evaluate strategies for preventing the transmission of other bloodborne infections through contaminated injecting equipment, such as hepatitis C. Furthermore, the Committee does not evaluate prevention strategies to reduce nosocomial HIV infections acquired from injecting equipment used in medical settings (e.g., through reuse of contaminated needles and syringes or accidental needle sticks resulting from improper disposal of needles and other sharps).

Finally, although the report focuses on HIV prevention for IDUs in high-risk countries, the Committee considered evidence from countries around the world. The findings and recommendations of this report are also applicable to countries where injecting drug use is not the primary driver, but in which injection drug use is nevertheless associated with significant HIV transmission.

ORGANIZATION OF THE REPORT

Chapter 1 reviews the epidemiology of HIV among IDUs, and discusses factors affecting HIV-related risks among IDUs. It also outlines major HIV prevention strategies for IDUs and their coverage. Chapters 2 and 3 provide the Committee's evaluation, conclusions, and recommendations on the major HIV prevention strategies highlighted in the charge. Chapter 2 reviews HIV prevention strategies that are part of treatment for drug dependence, including both pharmacotherapies and psychosocial interventions. Chapter 3 reviews evidence regarding sterile needle and syringe access programs, and outreach and education efforts. Chapter 4 summarizes the Committee's findings and highlights the importance of the local context—such as political, legal, and economic dimensions—in policy decisions, and provides recommendations that policymakers should consider when deciding which prevention programs to implement.

Several appendixes provide additional information on the following: the agenda of the Committee's December 2005 information-gathering meeting (Appendix A); methods used in the Committee's literature searches and review (Appendix B); case studies of HIV prevention for IDUs in select high-risk countries (Appendix C); summary of studies related to multicomponent HIV prevention programs that include needle and syringe exchange (Appendix D); additional thoughts on a community randomized trial of multi-component HIV prevention programs (Appendix E); and committee member biographies (Appendix F).

REFERENCES

Aceijas C, Stimson G, Hickman M, Rhodes T. 2004. Global overview of injecting drug use and HIV infection among injecting drug users. *AIDS*. 18:2295–2303.

DHHS (U.S. Department of Health and Human Services). 2006. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. [Online]. Available: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf [accessed August 3, 2006].

IOM (Institute of Medicine). 1990. *Treating Drug Problems: Volume 1*. Washington, DC: National Academy Press.

IOM. 1995. *Federal Regulation of Methadone Treatment*. Washington, DC: National Academy Press.

IOM. 1997. *Dispelling the Myths About Addiction*. Washington, DC: National Academy Press.

McLellan T, Lewis D, O'Brien C, Kleber H. 2000. Drug dependence, a chronic mental illness: Implications for treatment, insurance, and outcomes evaluation. *Journal of the American Medical Association*. 284(13):1689–1695.

UNAIDS (Joint United Nations Programme on HIV/AIDS). 2006. *2006 Report on the Global AIDS Epidemic: A UNAIDS 10th Anniversary Special Edition*. Geneva, Switzerland: UNAIDS.

WHO (World Health Organization), United Nations Office on Drugs and Crime, UNAIDS. 2004. *Substitution Maintenance Therapy in the Management of Opioid Dependence and HIV/AIDS Prevention: Position Paper*. Geneva, Switzerland: WHO.

1

HIV/AIDS in Injecting Drug Users

At the end of 2005, some 38.6 million people were living with HIV (UNAIDS, 2006). An estimated 4.1 million people were newly infected with HIV in 2005 (UNAIDS, 2006). While sub-Saharan Africa remains hardest hit by the HIV/AIDS epidemic, major epidemics are also emerging in other parts of the world, mainly as a result of injecting drug use. This report focuses on high-risk[1] countries—namely in Eastern Europe, the Commonwealth of Independent States, and significant parts of Asia—where injecting drug use is, or is on the verge of becoming, the primary driver of the HIV epidemic.

This chapter begins by exploring the epidemiology of HIV among injecting drug users (IDUs) in those regions, including prevalence of injecting drug use, prevalence of HIV among IDUs, and transmission routes. The chapter next focuses on the wide range of individual and structural (or environmental) factors that affect IDUs' risk of HIV infection. Examples of individual-level factors discussed in this chapter include severity of dependence, type of drug used, and existence and severity of co-occurring psychiatric disorders. Examples of structural-level factors include proximity to overland trafficking routes, drug laws and enforcement practices, injecting environment and culture, and stigma and discrimination.

The chapter then describes specific interventions to prevent HIV among

[1]In this report, such countries are labeled as "high-risk," indicating that injecting drug use is, or is on the verge of becoming, the primary driver of the HIV epidemic.

IDUs. The committee has grouped these interventions into three broad categories: drug dependence treatment (including both pharmacotherapies and psychosocial interventions), sterile needle and syringe access, and outreach and education. Other important HIV prevention and treatment strategies that are not specific to IDUs, such as voluntary counseling and testing, antiretroviral treatment, and prevention and treatment of sexually transmitted diseases, are also briefly discussed, but are not part of the committee's evidence review. The chapter ends with a brief discussion of the global coverage of HIV prevention services for IDUs.

EPIDEMIOLOGY OF HIV IN INJECTING DRUG USERS

Data on the size of the IDU population and HIV prevalence among IDUs are scarce. Estimating the size of the IDU population is difficult because drug use is an illegal and stigmatized activity. IDUs are often hidden and avoid settings where researchers might obtain data for fear of arrest or stigmatization (Magnani et al., 2005; Des Jarlais et al., 2001). HIV prevalence is difficult to estimate because many areas also lack the capacity to systematically monitor HIV infections among IDUs (Des Jarlais et al., 2001). Areas with routine HIV surveillance collect most of the data at institutions such as prisons, jails, and drug abuse treatment and outreach centers, which do not necessarily represent the IDU population at large (Dehne et al., 2002).

The United Nations Reference Group on HIV/AIDS Prevention and Care among IDUs recently developed estimates of the prevalence of injecting drug use, prevalence of HIV infection among IDUs, and the availability of prevention services worldwide, with a focus on developing and transitional countries (Aceijas et al., 2004). These estimates were compiled from a comprehensive review of published and unpublished documents for the period 1998–2003. Estimates were based on information available for 130 countries and territories.[2] The authors assigned a strength of evidence rating to each source based on the type of information and methods used in calculating the estimate. The strength of evidence supporting estimates of both IDU prevalence and HIV prevalence among IDUs was generally poor. Approximately 95 percent of the estimates of IDU prevalence and 64 percent of HIV prevalence estimates received a rating of "low," meaning that estimates lacked any supporting technical information (Aceijas et al., 2004). As a result of these limitations, estimates of IDU population size and HIV

[2]Data were missing for 119 countries and territories (Aceijas et al., 2004).

prevalence among IDUs should be interpreted with caution (Aceijas et al., 2004).

Based on these data, the UN Reference Group estimated that there are 13.2 million injecting drug users worldwide (Aceijas et al., 2004). Of those, an estimated 8.8 million live in Eastern Europe and Central, South, and Southeast Asia (Aceijas et al., 2004; UNAIDS, 2006), and an estimated 10.3 million (or 78 percent) live in developing or transitional countries (see Figure 1.1). A major driver of the rapid expansion of HIV in these and other areas is injecting drug use, accounting for about one-third of new infections outside sub-Saharan Africa. Worldwide, an estimated 10 percent of all HIV infections are related to injecting drug use, although that proportion is estimated to be much higher in certain regions of the world (UNODC, 2005; WHO, 2005a; Aceijas et al., 2004).

Primarily because of injecting drug use, Eastern Europe, Central Asia, and the Commonwealth of Independent States have witnessed as much as a 20-fold increase in the number of people living with HIV in less than a decade (UNAIDS, 2006). The majority of these individuals live in Ukraine and the Russian Federation. In Russia, an estimated 940,000 people were living with HIV at the end of 2005, and unsafe injecting practices are the main cause of HIV infection among people under the age of 30 (UNAIDS, 2006). In Ukraine, unsafe injecting practices and unprotected sex are both responsible for alarming increases in HIV infection. In some cities in Ukraine, 58 percent of IDUs are HIV-seropositive (UNAIDS, 2006). Young people are especially affected by the increase in HIV transmission among IDUs in the Commonwealth of Independent States, as many IDUs are below the age of 25 and began injecting before the age of 20 (UNAIDS, 2005).

Many other countries in Eastern Europe, Central Asia, and the Commonwealth of Independent States are also experiencing growing HIV epidemics. Currently, injecting drug use fuels the HIV epidemic in Uzbekistan, Kazakhstan, and Armenia (UNAIDS, 2006). Tajikistan is witnessing a smaller, yet rapidly evolving epidemic, illustrated by a study in its capital Dushanbe, which found an HIV prevalence of 12 percent among IDUs (Stachowiak et al., 2006). Sexual transmission continues to drive the epidemics of countries such as Belarus, Azerbaijan, Georgia, and Romania. However, both the continued increase in the number of injecting drug users and the rising HIV prevalence rates among both injecting drug users and sex workers could signal that a more generalized epidemic is looming (UNAIDS, 2006).

In Asia, an estimated 8.3 million people were living with HIV at the end of 2005, with India home to more than two-thirds of these individuals (UNAIDS, 2006). While sexual transmission is still the predominant route of transmission in India, injecting drug use is driving the epidemic in the

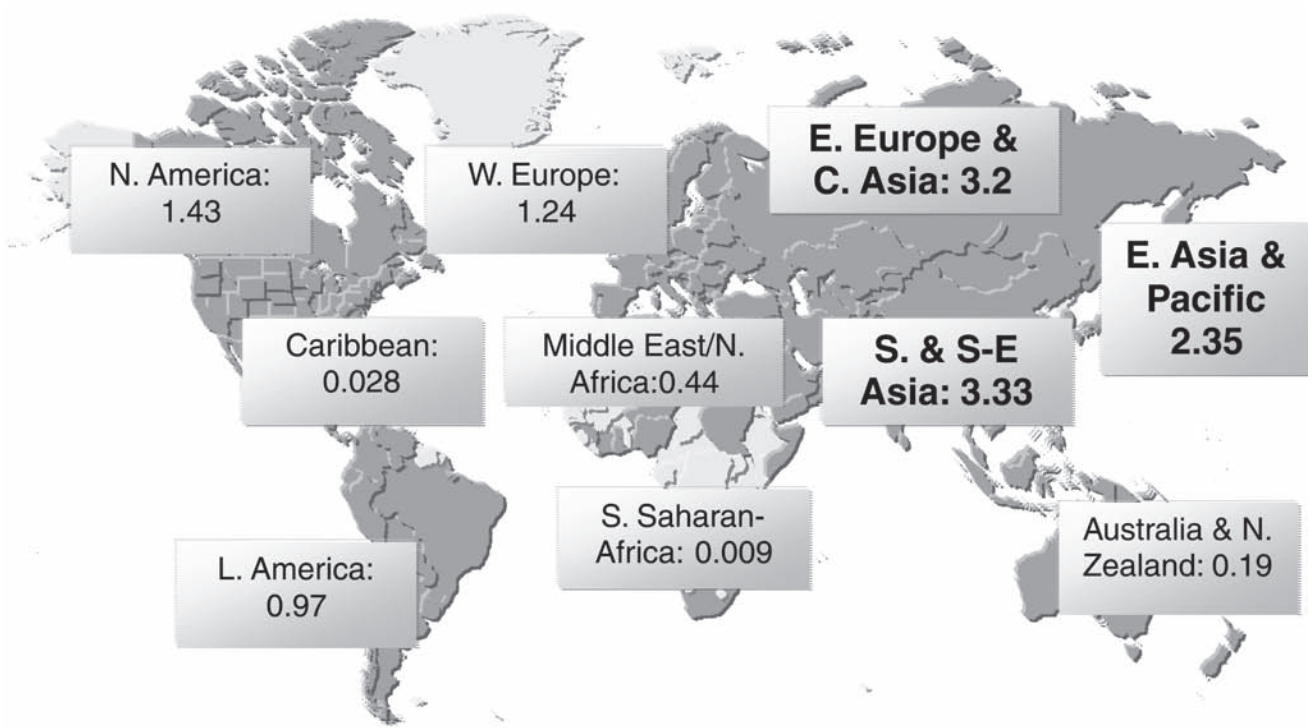

FIGURE 1.1 Estimates of IDU populations by region (in millions).
NOTE: Estimates are based on data collected from 130 countries from 1998–2003.
SOURCE: Reprinted, with permission, from the United Nations Office on Drugs and Crime, 2004 and the UN Reference Group on HIV/AIDS Prevention and Care among IDUs in Developing and Transitional Countries, 2004.

northeast states of Manipur, Mizoram, and Nagaland, and increasingly in the major cities of Chennai, Mumbai, and New Delhi (UNAIDS, 2006).

In Vietnam, injecting drug use and sex work are the main drivers of the HIV epidemic, with prevalence among IDUs rising from 9 percent in 1996 to 32 percent in 2003 (UNAIDS, 2006). Although Thailand has witnessed dramatic declines in the levels of HIV and sexually transmitted infections since the late 1990s, HIV among IDUs remains a major problem (UNAIDS, 2006).

As of September 2004, Malaysia had approximately 61,000 cases of HIV infection (Chawarski et al., 2006), with some 76 percent resulting from injecting drug use (WHO, 2003a). While the sharing of contaminated injecting equipment remains a large risk factor for HIV, sexual transmission, particularly in northern peninsular Malaysia, accounts for an estimated 12–56 percent of HIV infections among heroin users (Lye et al., 1994; Singh and Crofts, 1993). Other countries such as Indonesia and Bangladesh report low HIV prevalence among the general population, but the potential remains for explosive epidemics among high-risk groups such as IDUs and sex workers. Although data are very limited for Myanmar, an estimated one in three IDUs was HIV-seropositive in 2004 (UNAIDS, 2006).

In China, injecting drug users accounted for almost half of the people living with HIV in 2005 (UNAIDS, 2006). Sexual transmission has also grown substantially in the past few years, and evidence shows HIV infection spreading to the general population.

Injecting drug use is also driving the HIV epidemic in Iran, accounting for two-thirds of infections (Razzaghi et al., 2006). A recent study found that 15 percent of male IDUs attending drug treatment centers in Tehran were HIV-seropositive (UNAIDS, 2006).

Injecting drug use also accounts for a significant portion of HIV transmission in some countries outside these high-risk regions. In South America and the Caribbean, Brazil and Puerto Rico also report HIV prevalence among IDUs greater than 20 percent, as do some areas of Argentina and Uruguay (UNAIDS, 2006). Recent studies also suggest that injecting drug use is a growing problem that accounts for a small but increasing proportion of new HIV cases in Kenya, Nigeria, South Africa, Tanzania, Mauritius, and Egypt (Dewing et al., 2006; McCurdy et al., 2006; Beckerleg et al., 2005). In North America, approximately 20 percent of new infections in the United States in 2004 were attributed to injecting drug use (CDC, 2005). Canada's small HIV epidemic is driven by unprotected sex between men although HIV infection among women is rising, mostly due to unprotected sex and unsafe injecting drug use (UNAIDS, 2006). In Western and Central Europe, heterosexual transmission remains the driver of the HIV epidemic, while the epidemic in Australia and New Zealand is mainly driven by unprotected sex between men (UNAIDS, 2006).

BOX 1-1 Amphetamine-Type Stimulants

Methamphetamine and related amphetamine compounds (amphetamine-type stimulants, or ATS) are among the most commonly abused drugs, with an estimated 35 million users worldwide (Colfax and Shoptaw, 2005). These drugs target the central nervous system, increasing energy, alertness, disinhibition, and feelings of euphoria while decreasing appetite (Colfax and Shoptaw, 2005). Methamphetamine use can cause neurological toxicity, cardiovascular problems, dental decay, and skin infections (Colfax and Shoptaw, 2005). Chronic use is also associated with severe neurotoxicity and long-term cognitive impairment and mood disorders, although some cognitive functions can return after prolonged abstinence from the drug (Colfax and Shoptaw, 2005). Methamphetamine use is also associated with increased high-risk sexual behavior.

Use of ATS has grown rapidly in recent years, perhaps because ingredients are readily available in over-the-counter medicines (such as cough medicine), and large quantities can be easily produced in small, mobile laboratories (UNODC, 2002). Increases in ATS use are being reported in many areas of the world, with the most rapid expansions occurring in countries of Southeast Asia, including Hong Kong SAR, Indonesia, Thailand, Myanmar, Malaysia, Singapore, the Philippines, China, Lao People's Democratic Republic, Cambodia, and Vietnam. A major expansion of "yaba"—as amphetamines in tablet form are known in Thailand—prompted an intensive crackdown by the Thai government in its War on Drugs to decrease both supply and demand (Poshyachinda et al., 2005) (see Appendix C). ATS can be snorted, ingested, smoked, or injected, depending on the form in which the drug is available and cultural practices (UNODC, 2002). Most countries in Southeast Asia report that the preferred routes of administration are smoking, sniffing, and inhaling. However, the Philippines and Vietnam are reporting the injection of ATS (UNODC, 2002).

In addition to opiates[3] which are commonly injected, amphetamine-type stimulants and cocaine are also major injectable drugs of abuse in many high-risk countries (UNAIDS, 2006). Regions and countries vary widely in the types of drugs people use and their injecting behavior. In Latin America, for example, cocaine is the most commonly injected drug, although opium derivatives are increasingly available (Magis-Rodriguez et al., 2002). In Southeast Asia, methamphetamine production, trafficking, and use are rising dramatically, with an unknown percentage of users transitioning to injecting amphetamine use (see Box 1.1) (Kulsudjarit, 2004).

[3]"Opiates are a group of psychoactive substances derived from the poppy plant that includes opium, morphine, codeine and some others. The term 'opiate' is also used for the semisynthetic drug heroin that is produced from poppy compounds. The term 'opioids' refers to opiates and other semisynthetic and synthetic compounds with similar properties" (WHO et al., 2004, p. 4).

In South Asia, besides heroin, IDUs commonly inject synthetic painkillers, benzodiazepines, and other pharmaceuticals (Ghys, 2005).

ROUTES OF HIV TRANSMISSION

The sharing of contaminated injecting equipment is the primary mode of HIV transmission among IDUs, accounting for up to 80 percent of all HIV infections among IDUs in Eastern Europe and Central Asia (UNAIDS, 2006; UNODC, 2005). Sexual transmission from HIV-infected drug injectors to their sex partners is becoming an important secondary route of spread (Grassly et al., 2003), as is perinatal transmission from HIV-infected female IDUs or HIV-infected female sex partners of IDUs to their children.

Transmission Through Contaminated Injecting Equipment

HIV epidemics driven by injecting drug use tend to spread more rapidly than epidemics spread by sexual transmission, because exposure to the virus occurs more frequently, and because needles are more efficient at transmitting it than sex. In many parts of the world, HIV prevalence reached 40 percent and above among IDUs just 1 to 2 years after HIV entered the IDU population (Rhodes et al., 1999a). For example, in Edinburgh, an HIV outbreak started in 1983 among IDUs who had been injecting for only a year or two and spread rapidly through the IDU population, skyrocketing from 5 to 57 percent within 2 years (Robertson et al., 1986).

Examples of this trend also exist throughout Southeast Asia and Eastern Europe (Crofts et al., 1998; Rhodes et al., 1999b). A recent review concluded that HIV had spread rapidly in Belarus, Kazakhstan, Moldova, Russia, and Ukraine by the late 1990s, with 50–90 percent of new HIV infections occurring among IDUs (Rhodes et al., 1999b). While not the focus of this report, contaminated injecting equipment is also a mode of transmission for viral hepatitis (see Box 1.2).

Sexual Transmission

Sexual transmission from HIV-infected IDUs to their sex partners is becoming an important route of HIV transmission. Drug use is highly correlated with unsafe sexual practices, including unprotected sex, multiple partners, or exchanging sex for money or drugs (UNODC, 2005).

Many studies have found links between injecting drug use, commercial sex, and risky sexual behavior, resulting in high rates of HIV prevalence among sex workers who are also IDUs. Studies have shown that drug injecting sex workers are more willing to engage in unprotected sex, and

BOX 1-2 Viral Hepatitis

There are five identified types of viral hepatitis (A-E) and each one is caused by a different virus (CDC, 2003). Hepatitis C and B are the two most common types found among injecting drug users. Hepatitis C is an inflammation of the liver caused by the hepatitis C virus (HCV). Although the infection can be asymptomatic or mild, it can become chronic in over half of those infected. Among these, about half will eventually develop cirrhosis (scarring) or liver cancer (CDC, 2003). It is spread primarily by contact with the blood of an infected person, e.g., through receipt of contaminated blood or blood products, sharing needles or other injecting equipment, and through accidental needle-sticks or sharps exposures (CDC, 2003). Far less frequently it is spread sexually or from an infected mother to her baby. Recent studies show that HCV may survive on environmental surfaces at room temperature at least 16 hours, but not longer than 4 days (CDC, 2003). While there is regional variation, studies show that HCV prevalence among IDUs is often as high as 60 percent (Hagan, 1998; Garfein et al., 1998; Shapatava et al., 2006; Zhao et al., 2006). In addition to the sharing of needles and syringes, the sharing of other injecting and drug preparation equipment such as cookers used to melt drugs, cotton used to filter out particles when drawing the drug into the syringe, and water used to rinse syringes, has been associated with HCV infection (Diaz et al., 2001; Hagan et al., 1999, 2001; Hahn et al., 2002; Thorpe et al., 2002). There is no vaccine available for the prevention of HCV infection.

Hepatitis B is a disease caused by another bloodborne pathogen, the hepatitis B virus (HBV). HBV also produces liver inflammation and can cause lifelong infection, cirrhosis of the liver, liver cancer, liver failure, and death (CDC, 2003). Besides the potential for transmission through receipt of contaminated blood and blood products and through contact with other infectious bodily fluids (such as saliva or semen) and tissues, HBV is also spread through having unprotected sex with an infected person, by sharing drugs, needles, or other injecting equipment, through accidental needle-sticks or sharps exposures, or from an infected mother to her baby (CDC, 2003). It is stable on environmental surfaces for at least 7 days and has been transmitted between children living closely together in household settings. There is a vaccine to prevent HBV infection.

more likely to have a non-paying sex partner who is an IDU (Pisani et al., 2003; Paone et al., 1999).

National survey data also reveal a link between injecting drug use and high-risk sexual activity among commercial sex workers. In Ho Chi Minh City, Vietnam, 49 percent of injecting sex workers are infected with HIV, compared with 19 percent of those who use drugs but do not inject, and 8 percent of those who do not use drugs at all (MAP, 2005a). In Manipur, India, HIV prevalence was found to be 57 percent among sex workers who were also IDUs, compared with 20 percent among sex workers who did not inject drugs (Panda et al., 2001).

There are reports of high percentages of sex workers who also inject drugs. Estimates of the proportion of female sex workers who inject drugs include:

- From 25 to 80 percent in the Russian Federation (Lowndes et al., 2003).
- Some 30 percent across the Commonwealth of Independent States of the former Soviet Union (UNODC, 2005).
- Between 20 and 50 percent in Eastern Europe (UNODC, 2005).
- Between 10 and 25 percent in Central Asia (UNODC, 2005).

In addition, many IDUs sell sex as a means to obtain drugs or money to buy drugs (Lowndes et al., 2003). Data from several cities in countries such as Kazakhstan, Uzbekistan, and Kyrgyzstan show that while only a relatively small percentage of female sex workers in these cities inject drugs (6–14 percent), most female IDUs sell sex (56–67 percent) (MAP, 2005b). Studies in different Russian cities show that 15–50 percent of female IDUs are involved in sex work (Lowndes et al., 2003; Dehne and Kobyshcha, 2000).

Finally, some non-injecting women are infected with HIV by their injecting sexual partner or husband. In a study in Sao Paulo, 40 percent of non-injecting HIV-infected females had acquired the virus through unsafe sexual activity with IDUs (UNODC, 2005). In another study in India, 45 percent of non-injecting wives of HIV-seropositive IDUs were themselves infected with HIV, with 97 percent reporting sexual activity only with their husbands (Panda et al., 2000).

Perinatal Transmission

Perinatal transmission from infected female IDUs and infected partners of IDUs to their children is another growing concern. Transmission from a mother to a child can occur during pregnancy, labor and delivery, or breastfeeding (WHO, 2004a). The magnitude of IDU-associated perinatal transmission has not been systematically examined, but some studies suggest that it is a major problem. For example, according to one report, most HIV-infected infants born between 1996 and 2001 in the Russian Federation apparently had mothers who were either IDUs or sexual partners of IDUs (UNODC, 2005).

FACTORS INFLUENCING HIV RISK AMONG IDUS

A range of individual and structural factors can affect an IDU's risk of contracting HIV. Examples of factors specific to the individual include severity of drug dependence, preferred drug, and existence and severity of

co-occurring psychiatric disorders, among others. Structural factors contribute to the "risk environment" for injecting drug users, affecting their HIV-related risks and health outcomes by creating an environment in which HIV is more likely to be transmitted (Rhodes et al., 2005). Examples discussed in the following section include proximity to drug trafficking routes, drug laws and law enforcement practices, socioeconomic and political stability, injecting environment and culture, and stigma and discrimination.[4] Individual and structural factors converge to affect the likelihood that an IDU will engage in high-risk behavior, such as sharing of injecting equipment, more frequent injecting, commercial sex work, unprotected sex, and multiple sex partners.

Individual-Level Risk Factors

Severity of Dependence

Severity of dependence can influence the likelihood that someone will inject, the frequency of injection, and the sharing of contaminated equipment. Two studies by Gossop and colleagues using the same sample (n=408) examined the association between severity of heroin dependence with sharing injecting behavior and sexual behavior. One study (Gossop et al., 1993a) found that severity of heroin dependence was positively related to the occurrence and frequency of sex-for-money and sex-for-drugs transactions. The other study (Gossop et al., 1993b) found that more severely dependent heroin users were more likely to have shared injecting equipment. More dependent users also appeared to use heroin in private settings and to be at greater risk of sharing with dealers, possibly because of their urgent need during drug withdrawal. Other studies also found that severity of drug use, as measured by frequency of injection and injection of drug combinations, is significantly associated with sharing of equipment (Klee et al., 1990; Watters et al., 1994).

Type of Drug Used

The type of drug an IDU uses influences the frequency of injection and the risk of HIV transmission. An early epidemiological study in San Francisco found that injection cocaine use significantly increased the risk of HIV infection (Chaisson et al., 1989). Because cocaine has a relatively short half-

[4]See Rhodes et al. (2005) for a more comprehensive discussion of structural factors influencing the risk environment for IDUs.

life and is highly addictive, people may inject it more frequently, with reports of 10 times or more a day, compared with 1 to 3 injections per day among heroin-dependent IDUs (Chaisson et al., 1989). Even after controlling for frequency of use, Chaisson and colleagues found that cocaine injectors had a higher prevalence of HIV. They found that cocaine injection was associated with other behaviors that increased the risk of HIV: cocaine injectors were more likely to report sharing injecting equipment, using drugs in shooting galleries, and "booting" drugs (withdrawing blood into the syringe before injecting). Other studies in Montreal, Vancouver, and Toronto also found that cocaine use was positively associated with HIV infection (Bruneau et al., 2001; Strathdee et al., 2001, Lamothe et al., 1993).

Methamphetamine increases sexual drive and decreases inhibitions, leading to high-risk sexual behaviors (Colfax and Shoptaw, 2005). Methamphetamine use also increases the likelihood of engaging in high-risk sexual behavior such as unprotected sex and increased number of partners, and the acquisition of HIV and other sexually transmitted infections (Colfax and Shoptaw, 2005; Molitor et al., 1998; Molitor et al., 1999).

Presence and Severity of Co-Occurring Psychiatric Disorders

Co-occurring psychiatric disorders are common among drug-dependent individuals. Some psychiatric disorders precede the onset of drug dependence, while others are precipitated by chronic drug use (O'Brien et al., 2004). Opioid addicts have high rates of depression and antisocial personality disorder (Kosten and Rounsaville, 1986; Brooner et al., 1997). Similarly, cocaine abusers have high rates of affective and anxiety disorders, attention deficit disorder in childhood, and personality disorders (Schottenfeld et al., 1993). Methamphetamine users have high levels of depression, anxiety, and personality disorders (Chen et al., 2003; Zweben et al., 2004). Long-term methamphetamine use can also lead to psychosis (Chen et al., 2003), and amphetamine withdrawal commonly results in symptoms of severe depression (Urbina and Jones, 2004).

Studies have demonstrated a consistent positive association between psychiatric problems, particularly depressive disorders, and sharing of injecting equipment (Hawkins et al., 1998; Mandell at al., 1999). Depression may influence IDUs' risk of HIV infection by altering their perception of the threat of HIV infection, reducing their ability to judge the consequences of their decisions, decreasing their ability to cope with stressful events, and increasing the likelihood of careless behavior (Stein et al., 2003). Research has found that greater severity of depression is associated with increased sharing of injecting equipment, and the risk of acquiring or transmitting HIV (Stein et al., 2003).

Other psychopathologies also increase the risk for HIV infection. For example, in a study of cocaine users entering treatment (n=174), those with antisocial personality disorder (ASPD)[5] (35 percent of the sample) reported higher levels of sexual risk behaviors, and had more severe problems on the legal, alcohol, and psychiatric components of the Addiction Severity Index, than non-ASPD patients (Ladd and Petry, 2003).

Structural-Level Risk Factors

Proximity to Drug Trafficking Routes

Drug trafficking routes are also tightly linked with injecting drug use and HIV epidemics (Beyrer et al., 2000; Beyrer, 2002; Quan et al., 2000; Yu et al., 1999). The most apparent links lie along trafficking routes originating from the Golden Triangle of Southeast Asia (Myanmar, Laos, and Thailand) and from the Golden Crescent of Central Asia (Afghanistan, Pakistan, and Iran) (Chelala and Beyrer, 1999; Crofts et al., 1998; Poshyachinda, 1993; Qian et al., 2006). This factor is closely tied to shifts in drug production, which can lead to changes in drug transit routes. For example, increasing opium production in Afghanistan since 1989 has had an enormous impact on heroin availability throughout Central Asia (Todd et al., 2005).

Trafficking in methamphetamine accounts for the bulk of trafficking in amphetamine-type stimulants, and has been clearly shifting toward East and Southeast Asia. Myanmar is a major supplier of methamphetamine and serves as a source for Thailand and China. Seizures of methamphetamine are on the rise in China, mostly along its border with Myanmar (UNODC, 2004). Some reports indicate that ephedrine—used to illicitly manufacture methamphetamine in Southeast Asia—is diverted and smuggled out of China and India, whereas caffeine, used in making methamphetamine tablets, is mainly smuggled into Myanmar through its border with Thailand (Kulsudjarit, 2004). Growing demand for ecstasy (3,4-methylenedioxy methamphetamine), and the availability of precursor chemicals from China and Vietnam, provide evidence that nations in Southeast Asia may become havens for large-scale ecstasy manufacture. Significant laboratories have been discovered in China, Hong Kong, Taiwan, Malaysia, and, most notably, Indonesia (Kulsudjarit, 2004).

[5]ASPD is characterized by "poor social conformity and is associated with criminality, deceitfulness, irresponsibility, lack of remorse, and impulsivity" (American Psychiatric Association, 1994 as cited in Ladd and Petry, 2003).

Drug Laws and Law Enforcement

Drug laws and law enforcement practices have a complex influence on the HIV risk environment for IDUs. Burris and colleagues (2004) define *law* as having four components: (1) the law on the books—that is, statutes, constitutions, and regulations; (2) the management tools of criminal justice and law enforcement agencies, including training, policies, and standard operating procedures; (3) the "practices, knowledge, attitudes, and beliefs" of frontline personnel who enforce the laws (such as police officers); and (4) people's understanding of the laws (in this case the knowledge, attitudes, and beliefs of injecting drug users regarding laws).

Drug paraphernalia and drug possession laws have the most widespread impact on IDUs. Drug possession laws forbid the possession of a certain amount of illicit drugs. They can often be interpreted to include any measurable amount of drugs, including drug residue left in a used syringe (Burris et al., 2003). Drug paraphernalia is defined to include any equipment, product, or material that is intended for use in introducing controlled substances into the body. Drug paraphernalia laws ban the manufacture, sale, distribution, or possession of a wide range of such devices (Gostin, 1991). These laws do not prohibit the sale of equipment if it will not be used for injecting illicit drugs. For example, a diabetic could possess a needle/syringe if he/she could prove there is a valid medical purpose for possessing the equipment (Gostin, 1991).

Needle and syringe exchanges (NSEs) are illegal under general drug paraphernalia laws (Gostin et al., 1997) unless specific legislation exists to allow them or special permission is granted from local law enforcement authorities (Burris et al., 2002). Often the legal status of NSEs remains uncertain and consequently staff and participants may be arrested and legal action may be brought to close the NSE (Gostin et al., 1997).

Other laws that affect access to sterile needles and syringes include syringe prescription laws and pharmacy regulations. Syringe prescription laws prohibit persons from dispensing or possessing syringes without a valid medical prescription (Gostin et al., 1997). In addition, doctors must have a legitimate medical reason to prescribe syringes. Some prescription laws require pharmacists to maintain sales records (Gostin et al., 1997). Pharmacy regulations are not technically legally binding, but failure to comply may leave a pharmacist open to professional sanction (Gostin et al., 1997). Examples of pharmacy regulations could include requirements to maintain sales records or limits on the number of syringes sold at one time (Burris et al., 2003). In many cases, the decision to sell syringes is left to the discretion of the pharmacist and that decision may be influenced by uncertainty or lack of knowledge regarding the law (Burris et al., 2002). Furthermore, despite the legality of a pharmacist selling a syringe, the purchaser

may be violating syringe prescription or paraphernalia laws (Burris et al., 2002).

A number of studies have shown that drug laws and law enforcement practices can adversely affect HIV risks for IDUs, by limiting access to prevention services and deterring IDUs from participating (Rhodes et al., 2005; Burris et al., 2004; Hammett et al., 2005). If drug users do not have a sterile syringe when purchasing or injecting drugs, they are more likely to share injecting equipment (Gostin et al., 1997). A study in Vancouver found that the number of sterile syringes reaching IDUs declined more than 26 percent during a police operation that placed a constant and highly visible police presence near an NSE funded by the local health authority (Wood et al., 2003).

Laws and enforcement practices also shape the perceptions of IDUs and may increase their risk behaviors. For instance, fear of arrest for possessing needles and syringes reduces IDUs' participation in sterile needle and syringe access programs (Kral and Bluthenthal, 2004). Studies show that IDUs often fail to carry sterile syringes for fear of detection of such equipment by law enforcement (Gostin et al., 1997). Often drug users fear that if they are found carrying paraphernalia, the police have cause to search for illicit drugs which, if found, could lead to arrest and incarceration. In Russia, reluctance to carry needles and syringes because of fear of arrest for possessing drug paraphernalia was associated with a higher risk of needle and syringe sharing (Rhodes et al., 2003, 2004).

Because of syringe prescription laws or pharmacy regulations, persons purchasing syringes at pharmacies often have to present identification and sign a register (Burris et al., 2003). Drug users may avoid pharmacies because of the intrusive questioning and pharmacists may be reluctant to sell syringes because of fear of criminal penalties and professional sanctions. In China, even though IDUs have legal pharmacy access to syringes, they often fear that police monitor pharmacies (Singer et al., 2003).

In some countries, drug users are required to register with officials in order to receive drug treatment and other health and social services. These registries are sometimes shared with the police (ODCCP and UNAIDS, 2001), raising fears among and IDUs that registration will increase the chances of police detainment (Platt et al., 2004). For example, in Russia, registration could affect an IDU's ability to gain employment and secure housing (Platt et al., 2004) and could result in consequences related to employment status, citizenship, and residency rights (ODCCP and UNAIDS, 2001; Rhodes et al., 2003).

Many countries maintain a delicate balance between criminal justice approaches to combat drug use and public health programs to prevent HIV among IDUs (Hammett et al., 2005). An inherent tension exists between policies designed to enforce laws against illicit drug use and illegal activities

to support continued drug use, and public health approaches to mitigate health harms from drug use. For example, some may view HIV prevention programs that include sterile needle and syringe access as encouraging drug use or undermining police efforts to control access to drugs (NRC and IOM, 1995).

This tension suggests the need for more collaboration between public health and law enforcement officials to address the twin problems of drug use and HIV transmission (Hammett et al., 2005; Kozlov, 2006). As discussed in Chapter 4, public health and drug control officials need to work together to harmonize their policies while balancing their respective missions, and to increase communication and collaboration between police and health officials on the ground. This tension also points to the need to identify common ground and overlapping goals between these two approaches. Reconciling these roles can be difficult, but it is critical if HIV prevention efforts for IDUs are to succeed (Hammett et al., 2005).

Appendix C provides several case studies that illustrate how these two approaches to IDUs—criminal justice and public health—have played out at the national level in several high-risk countries.

Economic and Political Instability

Rapidly changing socioeconomic conditions, governmental transitions, and changes in transnational mobility stemming from border openings and new trade agreements can make populations more vulnerable to IDU outbreaks. For example, economic and social changes after Ukraine's independence left many people unemployed or earning only US$30–50 a month (Barcal et al., 2005). Selling hanka, a homemade opium solution, for US$0.95 per 1-milliliter dose during the poppy season, and US$1.50 out of season, quickly became a prosperous way to make a living, encouraging the spread of injecting opioid use (Barcal et al., 2005). Wars and other armed conflict can also spur drug production and alter or enhance drug distribution routes (Hankins et al., 2002).

Injecting Environment and Culture

The risk of HIV transmission is correlated with the context in which people inject drugs. IDUs who frequent shooting galleries, for example, are more likely to engage in risky behavior (such as needle sharing), and have been shown to have a higher risk of acquiring HIV (Magis-Rodriguez et al., 2005; Fuller et al., 2003; Hien et al., 2001). Shooting galleries are locations where IDUs can rent injecting equipment and use drugs. The equipment is usually not disinfected or cleaned before it is rented to the next user (McCoy and Inciardi, 1995). Professional injectors are IDUs who give injections to

other IDUs, often using the same needle on multiple clients, increasing the risk of HIV transmission (Kral et al., 1999).

The prevalence and burden of HIV/AIDS and other infectious diseases are higher in correctional facilities than in the general community (Hammett, 2006; Brown, 2005; Maruschak, 2002). A study in Tehran, Iran, recruited 213 IDUs to determine the prevalence and correlates of HIV infection (Zamani et al., 2006). In multivariate analyses, the study found that a history of sharing injecting equipment in prison (odds ratio [OR]=2.45; 95% confidence interval [CI] 1.01, 5.97) and multiple incarcerations (OR=3.13; 95% CI 1.08, 9.09) were associated with significantly higher prevalence of HIV infection.

Drug users are often over-represented in prisons, and, once incarcerated, many may continue using drugs (UNODC, 2005). IDUs in prisons share injecting equipment significantly more often than IDUs in the general community (Small et al., 2005). In prisons where possession of needles and syringes is prohibited, drug users often circulate their limited supply of injecting equipment, or even craft their own equipment out of common objects and pieces of old syringes (Small et al., 2005). Although coverage of HIV prevention interventions in prisons is limited, some prisons distribute condoms, bleach, and needles and syringes, or offer drug dependence treatment, risk reduction education, and voluntary counseling and testing (WHO, 2004b).

In addition to high-risk environments, a "culture of sharing" among IDUs can increase a user's likelihood of infection. Sharing is sometimes viewed as showing solidarity among IDUs, and is more common within tight-knit social networks, and between "running partners" and sexual partners (Des Jarlais et al., 1992). In addition to the social solidarity that sharing implies, drugs and injecting equipment are sometimes shared when users pool money to purchase larger quantities of drugs at cheaper prices. Other common reasons for sharing drugs and injecting equipment are the prevention of withdrawal, mediation of conflicts, or to reconcile financial debts (Grund et al., 1996). IDUs who are in the same social network often share food, money, information, and clothing, as well as provide each other with social support (Grund et al., 1996). Evidence shows that when knowledge of HIV/AIDS risks improves, and supplies of readily available sterile injecting equipment increase, syringe sharing falls, in accordance with a new ethics of "informed altruism" and "partner restriction." In such cases, sharing, if it occurs at all, will be more and more limited to sexual partners and other intimate acquaintances (Des Jarlais et al., 2004).

Stigma and Discrimination

Stigma occurs when an undesirable attribute reduces an individual's status in the eyes of society (Goffman, 1963). Stigma can result in discrimi-

nation, rejection, prejudice, and discounting of an individual or group. Stigma toward drug users can exist in many forms. A study by Dean and Rud (1984) found that the term "drug addict" evoked images of disorientated, thin, and unhealthy people with behavioral problems. Attitudes of health care professionals can discourage IDUs from seeking treatment (Ritson, 1999), as can attitudes of pharmacists toward IDUs seeking to purchase clean injecting equipment (Taussig et al., 2002). In Russia, IDUs who use drug treatment facilities are registered and then monitored for 5 years, and this registration can have everyday consequences such as restrictions on employment and social discrimination. Drug users cite stigma as a reason to avoid registration and drug treatment (Bobrova et al., 2006).

Drug-related stigma is often layered on top of other stigmas associated with specific groups, such as people living with HIV and commercial sex workers. Consequences of stigma can be viewed along a continuum from reactions including silence and denial to ostracism and violence. Research has shown that stigma can have a variety of negative effects on people's willingness to be tested for HIV, disclose their HIV status, and seek health care, as well as the quality of the health care and social support they solicit and receive (King, 1989; Malcolm et al., 1998; Raveis et al., 1998; Sowell et al., 1997).

HIV PREVENTION STRATEGIES

This section provides a brief overview of the HIV prevention strategies for IDUs. Because drug dependence is a chronic disease, most drug users experience repeated cycles of remission and resumption over extended periods of time (Hser et al., 1993, 2001). The chronic nature of drug dependence poses an enormous challenge to developing intervention policies and programs that effectively reduce HIV transmission—not just in the short term but also in the long term—among and from IDUs.

The most effective way for IDUs to reduce their risks of HIV infection is to stop using drugs. However, not all drug users are ready or able to stop using drugs. If they are not, a variety of strategies is available for preventing HIV infection, each designed for drug users at different points (see Box 1.3).

As noted, an individual IDU's risk of contracting and transmitting HIV is mediated by both individual-level and structural-level risk factors. The vast majority of HIV prevention efforts target the risk behavior of individual drug users, attempting to get them to: stop using drugs (through drug treatment); stop injecting (through drug treatment or education); use a clean needle (through sterile needle and syringe access programs); stop sharing equipment (through sterile needle and syringe access and education); disinfect each time (through disinfection programs and education); and to know their HIV status (through voluntary counseling and testing).

BOX 1-3 Hierarchy of Steps IDUs Can Take to Reduce HIV Risk

1. Stop using drugs.
2. Stop injecting drugs.
3. Always use a new, sterile syringe to inject drugs, and use sterile equipment to prepare drugs.
4. Never reuse or share syringes, water, or drug-preparation equipment.
5. Use bleach to properly disinfect injecting equipment.
6. Share supplies with as few other people as possible ("partner restriction").
7. Know your HIV status, and—if you are seropositive—do not pass on needles and syringes and use condoms during sex ("informed altruism") and seek antiretroviral therapy.
8. If you are an HIV-infected female who becomes pregnant, seek antiretroviral therapy to prevent perinatal transmission.

SOURCE: Adapted (with modifications by the Committee) from NIDA (2002) and Des Jarlais (2005).

Outreach and education complements each step of the hierarchy by serving to engage and foster the participation of IDUs. Structural-level interventions, which attempt to create an environment supportive of individual behavioral change, have not received sufficient attention from researchers and policymakers (Rhodes et al., 2005; Burris et al., 2004). Examples of structural-level interventions include law reform or programs to reduce stigma and discrimination against HIV-infected people or drug users While not the focus of the Committee's report, structural interventions are an important component of an effective HIV prevention response.

Although definitions vary, many health policy and research organizations recommend a comprehensive HIV prevention strategy for IDUs. According to the World Health Organization (WHO), a comprehensive HIV prevention program for IDUs includes outreach, information, education and communication, risk reduction counseling, HIV testing and counseling, disinfection programs, sterile needle and syringe access programs, disposal of used injecting equipment, drug treatment services, agonist pharmacotherapy programs, HIV/AIDS treatment and care, primary health care, and peer education (WHO, 2005a). According to the U.S. National Institute on Drug Abuse (NIDA, 2002), comprehensive programs encompass three approaches: community-based outreach, drug abuse treatment, and sterile needle and syringe access. These three approaches include a voluntary HIV counseling and testing component and may include many components cited by WHO. Although HIV prevention programs for IDUs rarely include just a single intervention, truly comprehensive programs are rare. Descriptions

of various specific components of a comprehensive approach are outlined below.

Treatment for Drug Dependence

Treatment for drug dependence can occur in a variety of settings including inpatient, outpatient, and residential venues, and often blends different approaches, including pharmacotherapies and psychosocial or behavioral interventions (WHO, 2005b). The efficacy and effectiveness of these strategies are discussed in Chapter 2.

Pharmacotherapies

No pharmacotherapies have been found to be consistently efficacious in treating stimulant dependence. Pharmacological agents are available, however, to treat opioid dependence. There are two primary types of opioid pharmacotherapies: agonist and antagonist medications.

Opioid agonist medications: These medications work by preventing withdrawal symptoms and reducing opiate cravings—and therefore the need to use illicit drugs—and also by diminishing the effects of opioid use by creating cross-tolerance to their effects (IOM, 1995). Agonist medications have two primary clinical applications; they can be used on a limited basis to facilitate opioid detoxification,[6] or they can be administered over a longer period as a maintenance treatment (IOM, 1995). When used to assist with detoxification, the agonist agent helps to relieve patient discomfort during withdrawal and the dosage is slowly tapered over time until the person reaches a drug-free state (IOM, 1990, 1995). Studies have demonstrated high rates of relapse when detoxification is not followed by further therapeutic intervention (IOM, 1990). Furthermore, because it lowers tolerance, detoxification can raise the risk of fatal overdose among individuals who resume opioid use (Strang et al., 2003).

In maintenance therapy, the agonist agent is administered at high doses for a sustained period. The goal of maintenance treatment is to reduce illicit drug use and high-risk behavior by building cross-tolerance to the effects of other opioids, thereby allowing patients to stabilize physiologically and psychologically, so they can reengage in normal life activities (IOM, 1990;

[6]Detoxification refers to medically supervised withdrawal to a drug-free state over a short period of time (typically 5–7 days, but up to several months). Pharmacological agents are often used during detoxification to reduce patient discomfort and the likelihood of complications (IOM, 1990).

WHO et al., 2004). Due to their long half life and resulting steady state, opioid agonists are not intoxicating and do not impair function when used at clinically appropriate and stable doses over time (IOM, 1990, 1995).

Methadone is the most widely used and researched agonist maintenance medication for the treatment of opioid dependence (WHO et al., 2004). Methadone is a synthetic, full opioid agonist; initially developed as an analgesic, it became a treatment for heroin dependence in the 1960s (IOM, 1995). Methadone is typically administered orally in liquid (syrup) form, but is also available in tablet form in some countries. Methadone can be administered once a day and prevents opioid withdrawal and provides cross-tolerance to the effects of other opioids for 24 hours in most patients (IOM, 1995). Methadone has a low incidence of side-effects and most patients entering treatment respond well (WHO et al., 2004). Because overdose is possible and methadone may be abused, it is generally administered to patients in controlled medical settings (e.g., specialized methadone clinics) (IOM, 1995).

Buprenorphine is a partial opioid agonist that is used increasingly as an alternative to methadone. Because buprenorphine tablets are not well absorbed if swallowed, it is administered sublingually (under the tongue) (WHO et al., 2004). Buprenorphine tablets take 3 to 15 minutes to dissolve in the mouth (Compton et al., 2006). Buprenorphine has long-lasting effects on opiate receptors, and can be administered on alternate days or three times a week (Fudala et al., 1990; Johnson et al., 1995). Buprenorphine has relatively few side effects (WHO et al., 2004). Buprenorphine has been widely used in France since 1996[7] and has been used in over 20 other countries (WHO, 2003b). It was recently approved by the U.S. Food and Drug Administration for distribution in office-based settings outside of dedicated drug abuse treatment programs (WHO, 2005b). Both methadone and buprenorphine are classified as psychotherapeutic medicines for substance dependence treatment programs on the WHO list of essential medicines (WHO, 2005c).

Opioid antagonist medications: An alternative to opioid agonists are antagonist agents which block the effects of opiates. Naltrexone, the most commonly used opioid antagonist drug, is used to help patients maintain long-term abstinence from opiates (WHO, 2005b). Oral naltrexone provides relatively long-lasting (up to 1–3 days depending on dose) blockades

[7]In response to concerns about diversion and misuse of buprenorphine, France is considering a controversial proposal to reclassify buprenorphine as a narcotic. The effect that this measure, if implemented, would have on treatment access and availability is unclear. [Online]. Available: http://opiateaddictionrx.info/whatsnew.asp?id=1186 [accessed July 31, 2006].

of euphoric or rewarding effects of heroin or other opioids, and thus may help prevent resumption of opiate use (O'Brien and Kampman, 2004). New long-acting, injectable formulations of naltrexone produce adequate opioid blockade for up to one month (Comer and Collins, 2002). Before beginning naltrexone treatment, patients must be detoxified (medically withdrawn from heroin or other opioids), because naltrexone will precipitate severe withdrawal symptoms in people physically dependent on opioids (O'Brien and Kampman, 2004). Naltrexone binds tightly to opiate receptors, but does not activate them or have any rewarding, mood-altering, or euphoric effects, or lead to withdrawal symptoms when it is discontinued (O'Brien and Kampman, 2004). Because naltrexone's blockade of opiate effects can be overridden by sufficiently large doses of opioids, naltrexone decreases but does not eliminate the risk of opioid overdose (O'Brien and Kampman, 2004). Patients who discontinue naltrexone are at greater risk for overdose if they resume opioid use (O'Brien and Kampman, 2004; Digiusto et al. 2004).

Psychosocial Interventions

A second major approach to drug treatment involves psychosocial interventions, which include a broad range of psychological and behavioral strategies, used either alone or in combination with pharmacotherapies and other medical or social interventions (Mayet et al., 2004). These interventions may be provided with varying levels of intensity, frequency, and duration using different approaches including outpatient, partial hospital, hospital, or residential-based programs. Psychosocial interventions may be delivered in individual or group settings, and may also include family members in order to address family functioning (e.g., through behavioral family therapy). Examples of psychosocial interventions include specific behavioral interventions (e.g., cognitive behavioral therapy, contingency management) as well as collection of program models (e.g., therapeutic communities, 12-step programs) (see Chapter 2, Box 2.2 for a description of these interventions).

Sterile Needle and Syringe Access

Several HIV prevention approaches provide IDUs with access to sterile needle and syringes, including needle and syringe exchange (NSE), disinfection programs, safe injecting facilities, syringe sales through pharmacies and vending machines, and syringe prescriptions from physicians. The efficacy and effectiveness of these strategies are discussed in Chapter 3.

Sterile needle and syringe access aims to increase the availability of sterile injecting equipment, remove contaminated needles from circulation

among IDUs, and prevent drug users from discarding used needles in the community, where others might use them or suffer needle sticks. Sterile needle and syringe access may also offer activities or referrals designed to encourage IDUs to stop using drugs.

Needle and syringe exchange is rarely, if ever, conducted as an isolated intervention—nearly all programs combine NSE with one or more of the following prevention strategies: outreach, risk reduction education, condom distribution, bleach distribution and education on needle disinfection, and referrals to substance-abuse treatment and other health and social services. As a result, the Committee refers to these combined programs as "multi-component HIV prevention programs that include needle and syringe exchange."

Prevention programs that include NSE may operate in fixed or mobile sites (e.g., mobile van). Rules on the number of needles and syringes that IDUs can exchange at one time vary—although recent trends are to ease such limits and shift to need-based distribution. Recent evidence from several countries suggests that secondary needle and syringe exchange is growing: that is, a participant redistributes supplies from an NSE to other IDUs in his or her social network who are unwilling or unable to access the NSE directly. Such practices have the potential to increase the number of IDUs with access to supplies of sterile injection equipment as well as expand the reach of peer education, risk reduction information, and referrals to other services (Stopka, 2006; Irwin et al., 2006).

NSEs may distribute other injecting equipment, such as cotton, sterile cookers, sterile water bottles, and alcohol wipes, as well as bleach, condoms, and health pamphlets (Lurie et al., 1993). Such programs often include a variety of other services, such as HIV counseling and testing, referrals to drug treatment and other medical and social services, and information on reducing the risk of HIV infection.

Outreach and Education

Outreach relies on peers and local health workers to identify IDUs, provide education on preventing HIV infection, and serve as guides to health and social services (WHO, 2004c). Outreach is particularly useful in targeting hard-to-reach IDUs (WHO, 2004c). Outreach workers may distribute information on HIV/AIDS, bleach kits for disinfecting injection equipment, and condoms. While some programs are linked to needle and syringe exchanges or drug treatment programs, outreach efforts often occur outside clinical settings and separate from other interventions. Personal interactions between outreach workers and clients can occur in various venues in a community, as workers gain the trust of IDUs and become recognized as a source of information on reducing HIV risk (WHO, 2004c).

The efficacy and effectiveness of outreach and education is discussed in Chapter 3.

Other HIV Prevention Strategies

Other HIV prevention programs are not specific to IDUs, but may provide important sources of information or links to health and social services for drug users. Examples of these interventions include voluntary counseling and testing, antiretroviral therapy, and prevention and treatment of sexually transmitted infections. While there is a large body of evidence evaluating the effectiveness and efficacy of these interventions, it was beyond the Committee's scope to review this evidence. Instead, a brief overview of these interventions is presented below.

Voluntary HIV Counseling and Testing

Voluntary counseling and testing (VCT) involves providing counseling to an individual to help make an informed choice about HIV testing. It also provides HIV education and is increasingly seen as an entry to other HIV/AIDS and drug abuse services (Liechty, 2004). VCT is among the most common type of HIV education program worldwide, and is often the entry point to other HIV/AIDS prevention programs for IDUs and other at-risk groups. The efficacy of HIV VCT has been clearly associated with decreases in risk behavior among individuals and couples, and among both HIV-infected and non-infected people (Voluntary HIV-1 Counseling and Testing Efficacy Study Group, 2000; Kamenga et al., 2000). According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), data from more than 70 countries show the number of people using these services grew from an estimated 4 million in 2001 to 16.5 million in 2005 (UNAIDS, 2006).

Despite being a common and effective HIV prevention method, developing countries have been somewhat slow to implement VCT (Motuvu et al., 2005). Factors limiting access to VCT include the stigma associated with HIV/AIDS and drug use, fear of prosecution for illicit drug use, low awareness of the risks of HIV infection and thus the relevance of VCT, and the distance, time, and cost required to engage in VCT. However, the removal of barriers to knowing one's HIV serostatus by providing free, anonymous, and rapid testing with same-day results, can substantially enhance the uptake of VCT services. (Morin et al., 2006). Many agencies and governments have urged the use of rapid tests for HIV (Arthur et al., 2005; Metcalf et al., 2005), with same-day results to encourage testing (Morin et al., 2006; Liang et al., 2005). Providing anonymous HIV VCT has been shown to lead to higher testing rates (Rennie and Behets, 2006).

Antiretroviral Therapy

Antiretroviral therapy (ART), when used appropriately, can reduce HIV-related morbidity and mortality, improve the quality of life, restore and preserve immunologic function, and suppress viral load (DHHS, 2006). Globally, antiretroviral drugs reach only one in five who need them, and only about 1.3 million people received ART in low- and middle-income countries in 2005 (UNAIDS, 2006).

Treating IDUs with ART poses unique treatment challenges due to the high rate of co-occurring medical and psychiatric conditions, limited access to HIV care, increased likelihood of medication side effects and toxicities, and interactions between ART and opioid agonist maintenance treatments (DHHS, 2006). IDUs typically have a high rate of morbidity and mortality that can be unrelated or related to HIV disease. For example, IDUs have increased rates of tuberculosis, infections, endocarditis, hepatitis B and C infection, and neurologic and renal disease (DHHS, 2006). The high rate of co-occurring mental illness among IDUs also complicates treatment (DHHS, 2006).

Efficacy of ART among IDUs is comparable to other populations. IDUs are often thought to be poor candidates for ART because of concerns about adherence during active drug use and underlying medical complications resulting from drug use (WHO, 2005d). IDUs are more likely to experience ART-related side-effects and toxicities perhaps due to the high degree of underlying medical problems (DHHS, 2006). Furthermore, clinical care of IDUs with HIV enrolled in opioid agonist treatment is complicated by the numerous pharmokinetic interactions between many ARTs and opioid agonist medications that can decrease the efficacy of one or the other treatments (DHHS, 2006). As a result, regimens need to be carefully selected and patients monitored for such interactions.

Studies have found that IDUs have limited access to and are less likely than other populations to receive ART (DHHS, 2006). In a study in Baltimore, factors associated with IDUs who report no ART include active drug use, lack of involvement in drug treatment, and recent incarceration (Celentano et al., 1998). In Vancouver, younger IDUs, females, IDUs not currently enrolled in drug treatment, and IDUs with inexperienced physicians were less likely to be receiving ART (Strathdee et al., 1998). Some studies show that IDUs are less likely to seek ART when it is available compared with non-IDUs (Strathdee et al., 1998; Celentano et al., 2001), especially when they are not participating in drug dependence treatment.

However, provision of successful ART to IDUs is possible. The success of HIV treatment is increased by provision of drug treatment, supportive providers who are familiar with unique health and social needs of IDUs, and an awareness of increased likelihood of ART side-effects and potential interactions with other therapies (DHHS, 2006).

HIV-seropositive pregnant women may receive ART both to treat their HIV infection and to prevent HIV infection in their infants (WHO, 2004a). The risk of mother-to-child transmission can be greatly reduced by providing antiretroviral drugs to women during pregnancy and labor and to the infant during the first weeks of life (WHO, 2004a). WHO has a set of recommendations regarding ART use during pregnancy to prevent mother-to-child transmission (WHO, 2004a). In resource-rich settings, WHO recommends triple-combination regimens to prevent perinatal transmission when the woman does not yet require ART. However, these regimens have not been fully evaluated in resource-limited settings. Short course antiretroviral drugs are currently recommended in resource-limited settings during late pregnancy or during labor, as well as for the infant after childbirth (WHO, 2004a).

Prevention and Treatment of Sexually Transmitted Infections

Early detection and treatment of sexually transmitted infections (STIs) greatly reduces the likelihood of sexual transmission of HIV (IOM, 1997). STIs increase the concentration of HIV in genital secretions and lesions and could also spark a more infectious variant of HIV (Cohen, 2004). In terms of susceptibility, STIs can cause lesions, inflammation, and produce a vaginal environment that is more conducive to HIV transmission (Cohen, 2004, 2006).

In particular, genital ulcers, especially genital herpes (herpes simplex virus type 2), syphilis (*Treponema pallidum*), and chancroid (*Haemophilus ducreyi*) greatly increase the risk of HIV infection (Wasserheit, 1992; Nelson et al., 1997; Serwadda et al., 2003). HIV infection has also been associated with reactivation of herpes simplex virus type 2. Herpes lesions provide a convenient entry point for HIV. A study in India found that individuals with newly acquired herpes simplex virus type2—the most common cause of genital ulcers—are at greatest risk for acquiring HIV, compared with those who do not have herpes simplex virus and those who have prevalent herpes simplex virus type 2 infection (Reynolds et al., 2003).

Non-ulcerative STIs are also associated with HIV transmission, perhaps by increasing the recruitment and activation of CD4+ cells (Laga et al., 1993; Royce et al., 1997). Vaginal infections are important risk factors for HIV acquisition. Both trichomonas and bacterial vaginosis have been associated with increased risk of HIV infection throughout sub-Saharan Africa (Gregson et al., 2001; Buve 2002).

The effectiveness of STI treatment for HIV prevention has been tested in Tanzania and Uganda. The study in Tanzania found that intensive clinical management of symptomatic STIs was associated with a 38 percent reduction in HIV incidence over 2 years (Grosskurth et al., 1995), while the

study in Uganda found that mass periodic treatment of STIs did not reduce HIV incidence (Wawer et al., 1999). Finally, Quinn and colleagues (2000) have shown that plasma viral load in one partner is highly associated with the sexual transmission of HIV to the uninfected partner, but antiretroviral therapy can reduce transmission risks substantially (Palella et al., 1998). Thus, the detection and appropriate medical management of common STIs remains one of the principal prevention strategies for reducing HIV risk in sexually active adults.

GLOBAL COVERAGE OF PREVENTION INTERVENTIONS

Coverage is a measure of the extent to which the services rendered cover the potential need for these services in a community (Last, 1995). Effective interventions could fail to prevent, control, or reduce the problem it seeks to address if a significant proportion of the population is not reached (Burrows, 2006). Estimates of the coverage of prevention interventions among IDUs are generally unreliable because of the uncertainty and limitations of the underlying data. As noted, estimates of the IDU population size (the denominator) often have a large margin of error. Data sources used to estimate the number of people reached by the service(s) (the numerator) also have limitations. National population surveys and facility-based surveys are the most reliable methods for estimating utilization, but are time-consuming and expensive to conduct (USAID et al., 2004). Service statistics can also be used, but data are often incomplete and less accurate than other sources. Furthermore, obtaining unduplicated estimates of program attendees from service statistics is difficult if service information systems are not designed to capture unique users (USAID et al., 2004).

Various organizations have set different coverage targets for HIV prevention programs. For example, the United Nations agencies recommend a minimum coverage target of 60 percent (i.e., the program should reach 60 percent of IDUs) for syringe distribution programs. A recent modeling study highlights the problem of setting universal coverage targets (Vickerman et al., 2006). While the model suggests that a coverage "threshold" exists which, if attained, can reduce HIV risk, the threshold depends on many factors such as frequency of injection, reuse of syringes, or the efficacy of disinfection.

Several studies have attempted to quantify the coverage of HIV prevention services for IDUs. According to a recent study of coverage of HIV/AIDS prevention, care, and support programs in low- and middle-income countries, an estimated 4.3 percent of the estimated 9–10 million IDUs living in these countries had access to HIV prevention programs (USAID et al., 2004). The most common type of program was risk reduction education (320,000 IDUs), followed by needle and syringe exchange (150,000

IDUs), and opioid agonist maintenance treatment (20,000 IDUs) (see Table 1-1). These estimates, however, are extrapolated from data in 24 countries that reported having prevention programs for IDUs in 2003. The remaining 64 countries included in the study (total n=88) did not report any coverage data because either injecting drug use was not prevalent or data were missing on program coverage or the size of the IDU population (USAID et al., 2004).[8] As a result, these estimates should be treated with caution.

A variety of other sources provide estimates of HIV prevention coverage for IDUs. The information below was compiled from multiple sources that do not use consistent definitions or timeframes, and therefore are not complete or comparable. However, they all suggest that coverage of prevention services for IDUs is limited.

Based on data collected by the UN Reference Working Group, 65 of 130 countries reporting injecting drug use have at least one sterile needle and syringe access program. However, programs have not been widely implemented in every country. Even when NSE does exist, the coverage is often poor. Results from a survey suggest that 65 percent of needle and syringe exchanges in Russia reach less than 1 percent of the local IDU population, and that fewer than 5 percent of projects reach more than 5 percent of their local IDU population (Burrows, 2001).

At least eight countries have reported NSEs in prisons (Switzerland, Germany, Spain, Armenia, Moldova, Kyrgyzstan, Belarus, and Iran) (Canadian HIV/AIDS Legal Network, 2004; Dolan et al., 2003; OSI, 2005). Programs are pending in Kazakhstan, Tajikistan, and Ukraine (Canadian HIV/AIDS Legal Network, 2004).

More than 19 developing and transitional countries have approved opioid agonist maintenance treatment (Hankins, 2005). However, the United States, United Kingdom, Spain, Germany, Italy, Canada, Australia, and Iran accounted for more than 85 percent of methadone consumption in 2004 (INCB, 2005). One recent study estimated that out of some 3 million IDUs, approximately 2,000 patients were receiving methadone or buprenorphine in 16 high-risk countries[9] in Central and Eastern Europe and the former Soviet Union. It also estimated that about 10,850 patients were receiving methadone or buprenorphine in 5 high-risk countries[10] in Asia out of roughly 2.2 million IDUs (OSI, 2005).

---

[8]A new report with updates of these figures is forthcoming.

[9]Countries included in this estimate: Armenia, Azerbaijan, Belarus, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Moldova, Poland, Russia, Tajikistan, Turkmenistan, Ukraine, and Uzbekistan (OSI, 2005).

[10]Countries included in this estimate: China, Indonesia, Iran, Malaysia, and Vietnam (OSI, 2005).

TABLE 1-1 Percent of Injecting Drug Users Covered by HIV Prevention Services in 2003, by Region

Region	Percent Coverage (weighted average)	Estimated Number of IDUs Receiving Information, Education, and Communication	Estimated Number of IDUs Receiving Needle and Syringe Exchange	Estimated Number of IDUs Receiving Opioid Agonist Maintenance Treatment	Number of Countries	Estimated Number of IDUs
African region	1.3%	1,500	—	250	4	79,000
Eastern Mediterranean region	21%	35,000	3,500	7,500	2	170,000
Eastern European region	7.6%	62,000	70,000	1,000	6	2,500,000
Region of the Americas	2.7%	8,300	16,000	—	3	900,000
Southeast Asia region	5.4%	83,000	59,000	11,000	4	1,250,000
Western Pacific region	2.9%	130,000	5,300	50	5	4,300,000
Total	4.3%	320,000	150,000	20,000	24	9,200,000

NOTE: Regional coverage is estimated as the weighted average of coverage for countries reporting data. The country values are weighted by the estimated number of injecting drug users in 2003. National estimates of the number of injecting drug users were used, when provided. Otherwise, regional averages for the percent of adults injecting drugs were used to estimate the number of IDUs.
SOURCE: Reprinted, with permission, from Constella Futures. Copyright 2004.

China is rapidly scaling up access to methadone maintenance treatment, with plans to treat over 300,000 patients in the next few years (Office of the State Council Working Committee on AIDS in China, 2005). On the other side of the spectrum, federal law in Russia prohibits the treatment of drug dependence with opioid agonist agents such as methadone. There is widespread opinion among the Russian narcotics community that methadone substitutes one addiction for another. Thus drug dependence treatment in Russia focuses on abstinence-based programs (Personal communication, V.N. Krasnov, Russian Society of Psychiatrists, June 16, 2006).

Some countries, such as Australia, Moldova, Indonesia, Poland, the United States, among others, have successfully provided methadone treatment, often on a pilot basis, in prison settings (OSI, 2005; Dolan et al., 2003). One example of a prison-based methadone program is at the New York City Correctional Facility at Rikers Island in the United States. The prison has operated a methadone maintenance program there since 1986 (Joseph et al., 1988). Eligible inmates are voluntarily enrolled from the detoxification wards into the KEEP (Key Extended Entry Process) program which stabilizes patients on methadone while in jail and then refers them to community-based KEEP methadone programs to continue their treatment upon release (Joseph, 1988). The goals of the Rikers Island program are to prevent inmate relapse into drug abuse upon release, to reduce the spread of HIV, and to initiate long-term treatment (Joseph, 1988).

Community-based outreach has been successful in making contact with large numbers of IDUs in North America, Western Europe, and Australia. However, few programs in developing and transitional countries are reaching the majority of IDUs through outreach services. Exceptions include Bangladesh, the Czech Republic, Kyrgyzstan, and Lithuania (WHO, 2004c). India has also implemented large-scale outreach programs in connection with needle and syringe exchange in some states, and Nepal has been conducting outreach activities for more than a decade in connection with its national NSE program (WHO, 2004c). While the Russian Federation experienced some early success with an outreach program in Kazan, which at one time extended across 101 sites and reached an estimated 7,700 IDUs, police activities have forced most of those sites to close (WHO, 2004c). In Latin America, Brazil and Argentina are the only countries that have achieved widespread IDU coverage through outreach. No countries in Africa or the Middle East have reported providing community-based outreach services to IDUs (WHO, 2004c).

CONCLUSION

Injecting drug use is a major factor in the continuing spread of HIV. This report focuses on high-risk countries—namely in Eastern Europe, the

Commonwealth of Independent States, and significant parts of Asia—where injecting drug use is, or is on the verge of becoming, the primary driver of the HIV epidemic. There are an estimated 13.2 million IDUs worldwide. Of those, an estimated 8.8 million live in Eastern Europe, Central, South, and Southeast Asia (Aceijas et al., 2004; UNAIDS, 2006), and an estimated 10.3 million (or 78 percent) live in developing or transitional countries. Primarily because of injecting drug use, Eastern Europe, Central Asia, and the Commonwealth of Independent States have witnessed as much as a 20-fold increase in the number of people living with HIV in less than a decade (UNAIDS, 2006). In Asia, an estimated 8.3 million people were living with HIV at the end of 2005, with rapidly expanding epidemics in both Central and particularly Southeast Asia from injecting drug use (UNAIDS, 2006).

Drug use behavior and the type of drugs used vary substantially across regions. HIV epidemics driven by injecting drug use tend to spread more rapidly than epidemics spread by sexual transmission, because exposure to the virus occurs more often, and because needles are more efficient at transmitting it than sex. In many parts of the world, HIV prevalence reached 40 percent and above among IDUs just 1 to 2 years after HIV entered the IDU population (Rhodes et al., 1999a). While sharing of contaminated injecting equipment is the primary mode of HIV transmission among IDUs, sexual transmission from HIV-infected drug injectors to their sex partners is becoming an important secondary route of spread (Grassly et al., 2003), as is perinatal transmission from HIV-infected female IDUs or HIV-infected partners of IDUs to their children.

Both individual-level factors (severity of dependence, preferred drug, presence and severity of psychiatric problems) and structural-level factors (proximity to drug trafficking routes, drug laws and enforcement practices, and stigma and discrimination) affect a drug user's risk of acquiring or transmitting HIV. Understanding these risk factors is critical to designing effective prevention programs. While many interventions focus on individual-level risk factors, few focus on structural-level factors (Rhodes et al., 2005).

There are many approaches to HIV prevention for IDUs available, and there are many permutations in their application. Three major categories of HIV prevention interventions for IDUs that are reviewed in this report include: drug dependence treatment programs, which include both pharmacotherapies and psychosocial interventions; sterile needle and syringe access programs; and outreach and education programs. Data on the coverage of these interventions are quite limited, but in general, estimates suggest that coverage is inadequate in many areas.

The next two chapters review the effectiveness regarding drug dependence treatment, sterile needle and syringe access, and outreach and education. By reviewing this evidence, the Committee hopes to provide up-to-

date information that policymakers in high-risk countries can use to decide how to best adopt and implement interventions to prevent HIV infection among IDUs.

REFERENCES

Aceijas C, Stimson GV, Hickman M, Rhodes T. 2004. Global overview of injecting drug use and HIV infection among injecting drug users. *AIDS*. 18(17):2295–2303.

American Psychiatric Association. 1994. *Diagnostic and Statistical Manual of Mental Disorders* (4th Ed.). Washington, DC: American Psychiatric Association.

Arthur GR, Ngatia G, Rachier C, Mutemi R, Odhiambo J, Gilks CF. 2005. The role for government health centers in provision of same-day voluntary HIV counseling and testing in Kenya. *Journal of Acquired Immune Deficiency Syndromes*. 40(3):329–335.

Barcal K, Schumacher JE, Dumchev K, Moroz LV. 2005. A situational picture of HIV/AIDS and injection drug use in Vinnitsya, Ukraine. *Harm Reduction Journal*. 2(1):16.

Beckerleg S, Telfer M, Hundt GL. 2005. The rise of injecting drug use in East Africa: A case study from Kenya. *Harm Reduction Journal*. 2:12.

Beyrer C. 2002. Human immunodeficiency virus (HIV) infection rates and heroin trafficking: Fearful symmetries. *Bulletin on Narcotics*. 44(1-2):103–116.

Beyrer C, Razak M, Lisam K, Chen J, Lui W, Yu XF. 2000. Overland heroin trafficking routes and HIV-1 spread in south and south-east Asia. *AIDS*. 14:75–83.

Bobrova N, Rhodes T, Power R, Alcorn R, Neifeld E, Krasiukov N, Latyshevskaia N, Maksimova S. 2006. Barriers to accessing drug treatment in Russia: A qualitative study among injecting drug users in two cities. *Drug and Alcohol Dependence*. 82(Suppl 1):S57–S63.

Brooner RK, King VL, Kidorf M, Schmidt CW, Bigelow GE. 1997. Psychiatric and substance use comorbidity among treatment-seeking opioid abusers. *Archives of General Psychiatry*. 54(1):71–80.

Brown K. 2005. Managing STIs in jails. *Infectious Diseases in Corrections Report*. 8:1–4. [Online]. Available: http://www.idcronline.org/archives/april05/article.html [accessed June 30, 2006].

Bruneau J, Lamothe F, Soto J, Lachance N, Vincelette J, Vassai A, Franco EL. 2001. Sex-specific determinants of HIV infection among injection drug users in Montreal. *Canadian Medical Association Journal*. 164(6): 767–773.

Burris S, Vernick J, Ditzler A, Strathdee S. 2002. The legality of selling or giving syringes to injection drug users. *Journal of the American Pharmaceutical Association*. 42(Suppl 2):S13–S18.

Burris S, Strathdee S, Vernick J. 2003. Lethal injections: The law, science, and politics of syringe access for injection drug users. *University of San Francisco Law Review*. 37: 813–885.

Burris S, Blankenship KM, Donoghoe M, Sherman S, Vernick JS, Case P, Lazzarini Z, Koester S. 2004. Addressing the "risk environment" for injection drug users: The mysterious case of the missing cop. *Milbank Quarterly*. 82(1):125–156.

Burrows D. 2001. *A Best Practice Model of Harm Reduction in the Community and in Prisons in the Russian Federation: Final Project Report*. Washington, DC: World Bank.

Burrows D. 2006. Rethinking coverage of needle exchange programs. *Substance Use and Misuse*. 41:1045–1048.

Buve A. 2002. HIV epidemics in Africa: What explains the variations in HIV prevalence? *International Union of Biochemistry and Molecular Biology: Life*. 53:193–195.

Canadian HIV/AIDS Legal Network. 2004. *Prison Needle Exchange: Lessons from a Comprehensive Review of International Evidence and Experience*. Toronto, Canada: Canadian HIV/AIDS Legal Network.

CDC (Centers for Disease Control and Prevention). 2003. *Viral Hepatitis*. [Online]. Available: http://www.cdc.gov/ncidod/diseases/hepatitis/index.htm [accessed August 24, 2006].

CDC. 2005. *HIV/AIDS Surveillance Report. 16*. [Online]. Available: http://www.cdc.gov/hiv/topics/surveillance/resources/reports/2004report/default.htm [accessed August 11, 2006].

Celentano D, Vlahov D, Cohn S, Shadle VM, Obasanjo O, Moore RD. 1998. Self-reported antiretroviral therapy in injection drug users. *Journal of the American Medical Association*. 280:544–546.

Celentano D, Galai N, Sethi A, Shah N, Strathdee S, Vlahov D, Gallant J. 2001. Time to initiate highly active antiretroviral therapy among HIV-infected injection drug users. *AIDS*. 15:1707–1715.

Chaisson RE, Bachetti P, Osmond D, Brodie B, Sande MA, Moss AR. 1989. Cocaine use and HIV infection in intravenous drug users in San Francisco. *Journal of the American Medical Association*. 261(4):61–65.

Chawarski MC, Mazlan M, Schottenfeld RS. 2006. Heroin dependence and HIV infection in Malaysia. *Drug and Alcohol Dependence*. 82(Suppl. 1):S39–S42.

Chelala C, Beyrer C. 1999. Drug use and HIV/AIDS in Burma. *Lancet*. 354(9184):1119.

Chen CK, Lin SK, Sham PC, Ball D, Loh EW, Hsiao CC, Chiang YL, Ree SC, Lee CH, Murray RM. 2003. Pre-morbid characteristics and co-morbidity of methamphetamine users with and without psychosis. *Psychological Medicine*. 33(8):1407–1414.

Cohen M. 2004. HIV and sexually transmitted diseases: Lethal synergy. *Topics in HIV Medicine*. 12(4): 104–107.

Cohen M. 2006. Thomas Parran Award Lecture: Transmission and prevention of transmission of HIV-1. *Sexually Transmitted Diseases*. 33(6):338–341.

Colfax G, Shoptaw S. 2005. The methamphetamine epidemic: Implications for HIV prevention and treatment. *Current HIV/AIDS Reports*. 2(4):194–199.

Comer SD, Collins ED. 2002. Self-administration of intravenous buprenorphine and the buprenorphine/naloxone combination by recently detoxified heroin abusers. *Journal of Pharmacology and Experimental Therapeutics*. 303(2):695–703.

Compton P, Ling W, Moody D, Chiang N. 2006. Pharmacokinetics, bioavailability and opioid effects of liquid versus tablet buprenorphine. *Drug and Alcohol Dependence* 82(1):25-31.

Crofts N, Reid G, Deany P. 1998. Injecting drug use and HIV infection in Asia: The Asian Harm Reduction Network. *AIDS*. 12(Suppl B):S69–S78.

Dean JC, Rud F. 1984. The drug addict and the stigma of addiction. *International Journal of Addiction*. 19:859–869.

Dehne K, Kobyshcha Y. 2000. *The HIV/AIDS Epidemic in Central and Eastern Europe: Update 2000*. Geneva, Switzerland: UNAIDS.

Dehne K, Adelekan M, Chatterjee A, Weiler G. 2002. The need for a global understanding of epidemiological data to inform human immunodeficiency virus (HIV) prevention among injection drug users. *Bulletin on Narcotics*. 44(1-2):117–130.

Des Jarlais DC. 2005 (December 20). *HIV Prevention for Injecting Drug Users: Lessons from North America*. Presentation at the Institute of Medicine Workshop on the Prevention of HIV Among Injecting Drug Users in High-Risk Countries, Geneva, Switzerland. Institute of Medicine Committee on the Prevention of HIV Infection Among Injecting Drug Users in High-Risk Countries.

Des Jarlais DC, Friedman SR, Choopanya K, Vanichseni S, Ward TP. 1992. International epidemiology of HIV and AIDS among injecting drug users. *AIDS*. 6:1053–1068.

Des Jarlais DC, Dehne K, Casabona J. 2001. HIV surveillance among injecting drug users. *AIDS*. 15(Suppl 3):S13–22.

Des Jarlais DC, Perlis T, Arasteh K, Hagan H, Milliken J, Braine N, Yancovitz S, Mildvan D, Perlman DC, Maslow C, Friedman SR. 2004. "Informed altruism" and "partner restriction" in the reduction of HIV infection in injecting drug users entering detoxification treatment in New York City, 1990–2001. *Journal of Acquired Immune Deficiency Syndromes*. 35:158–166.

Dewing S, Pluddemann A, Myers B, Parry C. 2006. Review of injection drug use in six African countries: Egypt, Kenya, Mauritius, Nigeria, South Africa and Tanzania. *Drugs: Education, Prevention and Policy*. 13(2):121–137.

DHHS (Department of Health and Human Services). 2006. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. [Online]. Available: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf [accessed August 3, 2006].

Diaz T, Des Jarlais DC, Vlahov D, Perlis T, Edwards V, Friedman S, Rockwell R, Hoover D, Williams I, Monterroso E. 2001. Factors associated with prevalent hepatitis C: Differences among young adult injection drug users in lower and upper Manhattan, New York City. *American Journal of Public Health*. 91(1):23–30.

Digiusto E, Shakeshaft A, Ritter A, O'Brien S, Mattick RP, NEPOD Research Group. 2004. Serious adverse events in the Australian national evaluation of pharmacotherapies for opioid dependence (NEPOD). *Addiction*. 99:450–460.

Dolan K, Rutter S, and Wodak AD. 2003. Prison-based syringe exchange programmes: A review of international research and development. *Addiction*. 98:153–158.

Fudala PJ, Jaffe JH, Dax EM, Johnson RE. 1990. Use of buprenorphine in the treatment of opioid addiction II: Physiologic and behavioral effects of daily and alternate-day administration and abrupt withdrawal. *Clinical Pharmacology and Therapeutics*. 47:525–534.

Fuller CM, Vlahov D, Latkin CA, Ompad DC, Celentano DD, Strathdee SA. 2003. Social circumstances of initiation of injection drug use and early shooting gallery attendance: Implications for HIV intervention among adolescent and young adult injection drug users. *Journal of Acquired Immune Deficiency Syndromes*. 32(1):86–93.

Garfein RS, Doherty MC, Monterrosso ER, Thomas DL, Nelson KE, Vlahov D. 1998. Prevalence and incidence of hepatitis C virus infection among young adult injection drug users. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*. 18(Suppl 1):S11–19.

Ghys P. 2005 (December 19). *Epidemiology of HIV Infection and AIDS among Injecting Drug Users*. Presentation at the Institute of Medicine Workshop on the Prevention of HIV Among Injecting Drug Users in High-Risk Countries, Geneva, Switzerland. Institute of Medicine Committee on the Prevention of HIV Infection Among Injecting Drug Users in High-Risk Countries.

Goffman, E. 1963. *Stigma: Notes on the Management of Spoiled Identity*. New York: Simon and Schuster.

Gossop M, Griffiths P, Powis B, Strang J. 1993a. Severity of heroin dependence and HIV risk. I. Sexual behaviour. *AIDS Care*. 5(2):149–157.

Gossop M, Griffiths P, Powis B, Strang J. 1993b. Severity of heroin dependence and HIV risk. II. Sharing injecting equipment. *AIDS Care*. 5(2):159–168.

Gostin L. 1991. An alternative public health vision for a national drug strategy: "Treatment works." *Houston Law Review*. 28(1):285–308.

Gostin L, Lazzarini Z, Jones S, Flaherty K. 1997. Prevention of HIV/AIDS and other bloodborne diseases among injection drug users: A national survey on the regulation of syringes and needles. *Journal of the American Medical Association*. 277:53–62.

Grassly NC, Lowndes CM, Rhodes T, Judd A, Renton A, Garnett GP. 2003. Modeling emerging HIV epidemics: The role of injecting drug use and sexual transmission in the Russian Federation, China, and India. *International Journal of Drug Policy*. 14:25–43.

Gregson S, Mason PR, Garnett GP, Zhuwau T, Nyamukapa CA, Anderson RM, Chandiwana SK. 2001. A rural HIV epidemic in Zimbabwe? Findings from a population-based survey. *International Journal of STDs and AIDS*. 12:89–96.

Grosskurth H, Mosha F, Todd J, Mwijarubi E, Klokke A, Swekoro K, et al. 1995. Impact of improved treatment of sexually transmitted disease on HIV infection in rural Tanzania: Randomised controlled trial. *Lancet*. 346:530–536.

Grund JP, Friedman S, Stern LS, Benny J, Neaigus A, Curtis R, Des Jarlais DC. 1996. Syringe-mediated drug sharing among injecting drug users: Patterns, social context and implications for transmission of blood-borne pathogens. *Social Science Medicine*. 42(5): 691–703.

Hagan H. 1998. Hepatitis C virus transmission dynamics in injection drug users. *Substance Use and Misuse*. 33:1197–1212.

Hagan H, McGough JP, Thiede H, Weiss NS, Hopkins S, Alexander ER. 1999. Syringe exchange and risk of infection with hepatitis B and C viruses. *American Journal of Epidemiology*. 149:203–213.

Hagan H, Thiede H, Weiss N, Hopkins S, Duchin J, Alexander ER. 2001. Sharing of drug preparation equipment as a risk factor for hepatitis C. *American Journal of Public Health*. 91(1):42–46.

Hahn JA, Page-Shafer K, Lum PJ, Bourgois P, Stein E, Evans J, Busch M, Tobler L, Phelps B, Moss AR. 2002. Hepatitis C virus seroconversion among young injection drug users: Relationships and risks. *Journal of Infectious Diseases*. 186:1558–1564.

Hammett TM. 2006. HIV/AIDS and other infectious disease among correctional inmates: Transmission, burden, and appropriate response. *American Journal of Public Health*. 96(3):13–17.

Hammett TM, Bartlett NA, Chen Y, Ngu D, Cuong DD, Phuong NM, Tho NH, Van LK, Donghua M, Shaomi X, Chen H, Quyen HN, Broadhead RS, Des Jarlais DC. 2005. Law enforcement influences on HIV prevention for injection drug users: observations from a cross-border project in China and Vietnam. *International Journal of Drug Policy*. 16: 235–245.

Hankins C. 2005 (December 19). *The Global Response to HIV and Injecting Drug Use*. Presentation at the Institute of Medicine Workshop on the Prevention of HIV Among Injecting Drug Users in High-Risk Countries, Geneva, Switzerland. Institute of Medicine Committee on the Prevention of HIV Infection Among Injecting Drug Users in High-Risk Countries.

Hankins CA, Friedman SR, Zafar T, Strathdee SA. 2002. Transmission and prevention of HIV and sexually transmitted infections in war settings: Implications for current and future armed conflicts. *AIDS*. 16:2245–2252.

Hawkins WE, Latkin C, Chowdury D, Hawkins MJ. 1998. Depressive symptoms and HIV-risk behaviour in inner-city users of drug injections. *Psychological Reports*. 82: 137–138.

Hien NT, Giang LT, Binh PN, Deville W, van Ameijden EJC, Wolffers I. 2001. Risk factors of HIV infection and needle sharing among injecting drug users in Ho Chi Minh City, Vietnam. *Journal of Substance Abuse*. 13:45–58.

Hser YI, Anglin D, Powers K. 1993. A 24-year follow-up of California narcotics addicts. *Archives of General Psychiatry*. 50:577–584.

Hser YI, Grella CE, Hubbard RL, Hsieh SC, Fletcher BW, Brown BS, Anglin MD. 2001. An evaluation of drug treatments for adolescents in 4 U.S. cities. *Archives of General Psychiatry*. 58(7):689–695.

INCB (International Narcotics Control Board). 2005. *Part Four: Statistical Information on Narcotic Drugs*. [Online]. Available: http://www.incb.org/pdf/e/tr/nar/2004/narcotics_part4.pdf [accessed June 30, 2006].

IOM (Institute of Medicine). 1990. *Treating Drug Problems: Volume 1*. Washington, DC: National Academy Press.

IOM. 1995. *Federal Regulation of Methadone Treatment*. Washington, DC: National Academy Press.

IOM. 1997. *The Hidden Epidemic: Confronting Sexually Transmitted Diseases*. Washington, DC: National Academy Press.

Irwin K, Karchevsky E, Heimer R, Badrieva L. 2006. Secondary syringe exchange as a model for HIV prevention programs in the Russian Federation. *Substance Use and Misuse*. 41: 979–999.

Johnson RE, Eissenberg T, Stitzer ML, Strain EC, Liebson IA, Bigelow GE. 1995. Buprenorphine treatment of opioid dependence: Clinical trial of daily versus alternate-day dosing. *Drug and Alcohol Dependence*. 40(1):27-35.

Joseph H. 1988. The criminal justice system and opiate addiction: A historical perspective. *NIDA Research Monograph*. 86:106–125.

Joseph H, Appel P, Marx R, Perez J, Tardalo F, Watts L. 1988. *Evaluation of Pre-KEEP in Three Facilities of the New York City Department of Corrections on Rikers Island. Treatment Issues Report*. New York: New York State Division of Substance Abuse Services.

Kamenga MC, Sweat MD, De Zoysa I, et al. 2000. The Voluntary HIV-1 Counseling and Testing Efficacy Study: Design and methods. *AIDS and Behavior*. 4(1):5–13.

King MB. 1989. Prejudice and AIDS: The views and experience of people with HIV infection. *AIDS Care*. 1(2):137–143.

Klee H, Faugier J, Hayes C, Boulton T, Morris J. 1990. Factors associated with risk behaviour among injecting drug users. *AIDS Care*. 2:133–145.

Kosten TR, Rounsaville BJ. 1986. *Psychopathology in opioid addicts. The Psychiatric Clinics of North America*. 9(3):515–532.

Kozlov AP. 2006. Uncertainty in descriptions of biosocial phenomena and the schism between preventionists and moralists. *Medical Hypotheses*. 67:662–665.

Kral A, Bluthenthal R. 2004. *The Pmpact of Police Practices on the Health of IDUs in the San Francisco Bay Area*. Abstract No. 1140. Presented at the 15th International Conference on the Reduction of Drug-Related Harm, Melbourne, 20–24 April.

Kral AH, Bluthenthal RN, Erringer E, Lorvick J, Edlin BR. 1999. Risk factors among IDUs who give injections to or receive injections from other drug users. *Addiction*. 94(5): 675–683.

Kulsudjarit K. 2004. Drug problem in southeast and southwest Asia. *Annals of the New York Academy of Sciences*. 1025:446–457.

Ladd GT, Petry NM. 2003. Antisocial personality in treatment-seeking cocaine abusers: Psychological functioning and HIV risk. *Journal of Substance Abuse Treatment*. 24: 323–330.

Laga M, Manoka A, Kivuvu M, et al. 1993. Non-ulcerative sexually transmitted diseases as risk factors for HIV-1 transmission in women: Results from a cohort study. *Journal of Infectious Diseases*. 7:95–102.

Lamothe F, Bruneau J, Coates R, Rankin JG, Soto J, Arshinoff R, Brabant M, Vincelette J, Fauvel M. 1993. Seroprevalence of and risk factors for HIV-1 infection in injection drug users in Montreal and Toronto: A collaborative study. *Canadian Medical Association Journal*. 149(7):945–951.

Last J. 1995. *A Dictionary of Epidemiology*. 3rd edition. New York: Oxford University Press.

Liang TS, Erbelding E, Jacob CA, Wicker H, Christmyer C, Brunson S, Richardson D, Ellen JM. 2005. Rapid HIV testing of clients of a mobile STD/HIV clinic. *AIDS Patient Care and STDs*. 19(4):253–257.

Liechty CA. 2004. The evolving role of HIV counseling and testing in resource-limited settings: HIV prevention and linkage to expanding HIV care access. *Current HIV/AIDS Reports*. 1(4):181–185.

Lowndes C, Alary M, Platt L. 2003. Injection drug use, commercial sex work, and the HIV/STI epidemic in the Russian Federation. *Sexually Transmitted Diseases*. 30(1):46–48.

Lurie P, Reingold AL, Bowser B, Chen D, Foley J, Guydish J, Kahn JG, Lane S, Sorensen J. 1993. *The Public Health Impact of Needle Exchange Programs in the United States and Abroad*. Volume 1. San Francisco: University of California.

Lye MS, Archibald C, Ghazali AA, Low BT, Sinniah M, Rus SC, Singh J, Nair RC. 1994. Patterns of risk behavior for patients with sexually transmitted diseases and surveillance for HIV in Kuala Lumpur, Malaysia. *International Journal of STDs and AIDS*. 5: 124–129.

Magis-Rodriguez C, Marques LF, Touze G. 2002. HIV and injection drug use in Latin America. *AIDS*. 16(Suppl 3):S34–S41.

Magis-Rodriguez C, Brouwer KC, Morales S, Gayet C, Lozada R, Ortiz-Mondragon R, Ricketts EP, Strathdee SA. 2005. HIV prevalence and correlates of receptive needle sharing among injection drug users in the Mexican-U.S. border city of Tijuana. *Journal of Psychoactive Drugs*. 37(3):333–339.

Magnani R, Sabin K, Saidel T, Heckathorn D. 2005. Review of sampling hard-to-reach and hidden populations for HIV surveillance. *AIDS*. 19(Suppl 2):S67–S72.

Malcolm A, Aggleton P, Bronfman M, Galvao J, Mane P, Verrall J. 1998. HIV-related stigmatization and discrimination: Its forms and contexts. *Critical Public Health*. 8(4): 347–370.

Mandell W, Joohyng K, Latkin C, Suh T. 1999. Depressive symptoms, drug networks, and their synergistic effect on needle-sharing behavior among street injection drug users. *American Journal of Drug and Alcohol Abuse*. 25(1):117–127.

MAP (Monitoring the AIDS Pandemic). 2005a. *Sex Work and HIV/AIDS in Asia*. Washington, DC: MAP.

MAP. 2005b. *Drug Injection and HIV/AIDS in Asia*. Washington, DC: MAP.

Maruschak LM. 2002. *HIV in Prisons, 2000*. Washington, DC: Bureau of Justice Statistics.

Mayet S, Farrell M, Ferri M, Amato L, Davoli M. 2004. Psychosocial treatment for opiate abuse and dependence. *Cochrane Database of Systematic Reviews*. (4):CD004330.

McCoy CB, Inciardi J. 1995. *Sex, Drugs, and the Continuing Spread of AIDS*. Los Angeles, CA: Roxbury.

McCurdy SA, Ross MW, Kilonzo GP, Leshabari MT, Williams ML. 2006. HIV/AIDS and injection drug use in the neighborhoods of Dar es Salaam, Tanzania. *Drug and Alcohol Dependence*. 82(Suppl 1):S23–S27.

Metcalf CA, Douglas JM Jr, Malotte CK, Cross H, Dillon BA, Paul SM, Padilla SM, Brookes LC, Lindsey CA, Byers RH, Peterman TA. 2005. Relative efficacy of prevention counseling with rapid and standard HIV testing: A randomized, controlled trial (RESPECT-2). The RESPECT-2 Study Group. *Sexually Transmitted Diseases*. 32(2):130–138.

Molitor F, Traux S, Ruiz J, Sun R. 1998. Association of methamphetamine use during sex with risky sexual behaviors and HIV infection among non-injection drug users. *The Western Journal of Medicine*. 168:93–97.

Molitor F, Ruiz J, Flynn N, Mikanda J, Sun R, Anderson R. 1999. Methamphetamine use and sexual and injection risk behaviors among out-of-treatment injection drug users. *American Journal of Drug and Alcohol Abuse*. 25(3):475–493.

Morin SF, Khumalo-Sakutukwa G, Charlebois ED, Routh J, Fritz K, Lane T, Vaki T, Fiamma A, Coates TJ. 2006. Removing barriers to knowing HIV status: Same-day mobile HIV testing in Zimbabwe. *Journal of Acquired Immune Deficiency Syndromes*. 41(2): 218–224.

Motuvu JK, Gray RH, Makumbi F, Wawer MJ, Serwadda D, Kigozi G, Sewankambo NK, Nalugoda F. 2005. Voluntary HIV counseling and testing acceptance, sexual risk behavior and HIV incidence in Rakai, Uganda. *AIDS*. 19(5):503–511.

Nelson KE, Celentano DD, Eiumtrakul S, et al. 1997. The association of herpes simplex-type 2, *Haemophilus ducreyi,* and syphilis infections with genital ulcer disease and HIV infection among young men in northern Thailand. *Journal of Acquired Immune Deficiency Syndromes*. 16:293–300.

NIDA (National Institute on Drug Abuse). 2002. *Principles of HIV Prevention in Drug-Using Populations: A Research-Based Guide*. Washington, DC: NIDA. [Online]. Available: http://www.nida.nih.gov/POHP/FAQ_1.html [accessed June 22, 2006].

NRC (National Research Council) and IOM (Institute of Medicine). 1995. *Preventing HIV Transmission: The Role of Sterile Needles and Bleach*. Washington, DC: National Academy Press.

O'Brien C, Kampman K. 2004. Opioids: Antagonists and partial agonists. In: *The American Psychiatric Association Textbook of Substance Abuse Treatment*. 3rd edition. Washington, DC: American Psychiatric Press, Inc. Pp. 305–319.

O'Brien CP, Charney DS, Lewis L, Cornish JW, Post RM, Woody GE, Zubieta JK, Anthony JC, Blaine JD, Bowden CL, Calabrese JR, Carroll K, Kosten T, Rounsaville B, Childress AR, Oslin DW, Pettinati HM, Davis MA, Demartino R, Drake RE, Fleming MF, Fricks L, Glassman AH, Levin FR, Nunes EV, Johnson RL, Jordan C, Kessler RC, Laden SK, Regier DA, Renner JA Jr, Ries RK, Sklar-Blake T, Weisner C. 2004. Priority actions to improve the care of persons with co-occurring substance abuse and other mental disorders: A call to action. *Biological Psychiatry*. 56(10):703–713.

ODCCP (Office of Drug Control and Crime Prevention) and UNAIDS. 2001. *Drug Abuse and HIV/AIDS: Lessons Learned—Case Studies in Central Eastern Europe and Central Asia*. New York: United Nations.

Office of the State Council Working Committee on AIDS in China. 2005. *Progress on Implementing UNGASS Declaration of Commitment in China 2005*. [Online]. Available: http://data.unaids.org/pub/Report/2006/2006_country_progress_report_china_en.pdf [accessed June 30, 2006].

OSI (Open Society Institute). 2005. *Harm Reduction Developments 2005. Countries with Injection-Driven HIV Epidemics*. New York: Open Society Institute.

Palella FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. 1998. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *New England Journal of Medicine*. 338:853–860.

Panda S, Chatterjee A, Bhattacharya SK, Manna B, Singh PN, Sarkar S, Naik TN, Chakrabarti S, Detels R. 2000. Transmission of HIV from injection drug users to their wives in India. *International Journal of STDs and AIDS*. 11:468–473.

Panda S, Bijaya L, Sadhana Devi N, Foley E, Chatterjee A, Banerjee D, Naik TN, Saha MK, Bhattacharya SK. 2001. Interface between drug use and sex work in Manipur. *National Medical Journal of India*. 14(4):209–211.

Paone D, Cooper H, Alperen J, Shi Q, Des Jarlais DC. 1999. HIV risk behaviour of current sex workers attending syringe exchange: The experiences of women in five US cities. *AIDS Care*. 11(3):269–280.

Pisani E, Dadun, Sucahya PK, Kamil O, Jazan S. 2003. Sexual behavior among injection drug users in 3 Indonesian cities carries a high potential for HIV spread to noninjectors. *Journal of Acquired Immune Deficiency Syndromes*. 34(4):403–406.

Platt L, Hickman M, Rhodes T, Mikhailova L, Karavashkin V, Vlasov A, Tilling K, Hope V, Khutorksoy M, Renton A. 2004. The prevalence of injecting drug use in a Russian city: Implications for harm reduction and coverage. *Addiction*. 99:1430–1438.

Poshyachinda V. 1993. Drug injecting and HIV infection among the population of drug abusers in Asia. *Bulletin on Narcotics*. 45(1):77–90.

Poshyachinda V, Ayudhya SNA, Aramrattana A, Kanato M, Assanangkornchai S, Jitipiromsri S. 2005. Illicit substance supply and abuse in 2000–2004: An approach to assess the outcome of the war on drug operation. *Drug and Alcohol Review*. 24:461–466.

Qian H, Schumacher J, Chen H, Ruan Y. 2006. Injection drug use and HIV/AIDS in China: Review of current situation, prevention and policy implications. *Harm Reduction Journal*. 3:4.

Quan VM, Chung A, Long HT, Donder TJ. 2000. HIV in Vietnam: The evolving epidemic and the prevention response, 1996–1999. *Journal of Acquired Immune Deficiency Syndromes*. 25:360–369.

Quinn TC, Wawer MJ, Sewankambo N, Servadda D, Li C, Wabwire-Mangen et al. 2000. Viral load and heterosexual transmission of Human Immunodeficiency Virus Type 1. Rakai Project Study Group. *New England Journal of Medicine*. 342:921–929.

Raveis VH, Siegel K, Gorey E. 1998. Factors associated with HIV-infected women's delay in seeking medical care. *AIDS Care*. 10(5):549–562.

Razzaghi EM, Movaghar AR, Green TC, Khoshnood K. 2006. Profiles of risk: A qualitative study of injecting drug users in Tehran, Iran. *Harm Reduction Journal*. 3:12.

Rennie S, Behets F. 2006. Desperately seeking targets: The ethics of routine HIV testing in low-income countries. *Bulletin of the World Health Organization*. 84:52–57.

Reynolds S, Risbud A, Shepherd M, Zenilman J, Brookmeyer R, Paranjape R, Divekar A, Gangakhedkar R, Ghate M, Bolllinger R, Mehendale S. 2003. Recent herpes simplex virus type 2 infection and the risk of human immunodeficiency virus type 1 acquisition in India. *Journal of Infectious Diseases*. 187:1513–1521.

Rhodes T, Stimson GV, Crofts N, Ball A, Dehne K, Khodakevich L. 1999a. Drug injecting, rapid HIV spread, and the "risk environment": Implications for assessment and response. *AIDS*. 13 (Suppl A):S259–S269.

Rhodes T, Ball A, Stimson GV, Kobyshcha Y, Fitch C, Pokrovsky V, Bezruchenko-Novachuk M, Burrows D, Renton A, Andrushckak L. 1999b. HIV infection associated with drug injecting in the newly independent states, eastern Europe: The social and economic context of epidemics. *Addiction*. 94(9):1323–1336.

Rhodes T, Mikhailova L, Sarang A, Lowndes CM, Rylkov A, Khutorskoy M, Renton A. 2003. Situational factors influencing drug injecting, risk reduction and syringe exchange in Togliatti City, Russian Federation: A qualitative study of micro risk environment. *Social Science Medicine*. 57(1):39–54.

Rhodes T, Sarang A, Bobrik A, Bobkov E, Platt L. 2004. HIV transmission and HIV prevention among injecting drug users in Russia. *International Journal of Drug Policy*. 15(1): 1–16.

Rhodes T, Singer M, Bourgois P, Friedman SR, Strathdee SA. 2005. The social structural production of HIV risk among injecting drug users. *Social Science Medicine*. 61(5):1026–1044.

Ritson EB. 1999. Alcohol, drugs, and stigma. *International Journal of Clinical Practice*. 53:549–551.

Robertson JR, Bucknall AB, Welsby PD, Roberts JJ, Inglis JM, Peutherer JF, Brettle RP. 1986. Epidemic of AIDS-related virus (HTLV-III/LAV) infection among intravenous drug users. *British Medical Journal*. 292(6519):527–529.

Royce RA, Sena A, Cates W, Cohen MS. 1997. Sexual transmission of HIV. *New England Journal of Medicine*. 336(15):1072–1078.

Schottenfeld R, Carroll K, Rounsaville B. 1993. Comorbid psychiatric disorders and cocaine abuse. *NIDA Research Monograph*. 135:31–47.

Serwadda D, Gray RH, Sewankambo N, Wabwire-Mangen F, Chen MZ, Quinn TC, Lutalo T, Kiwanuka N, Kigozi G, Nalugoda F, Meehan MP, Morrow AR, Wawer MJ. 2003. Human immunodeficiency virus acquisition associated with genital ulcer disease and herpes simplex virus type 2 infection: A nested case-control study in Rakai, Uganda. *Journal of Infectious Diseases*. 188(10):1492–1497.

Shapatava E, Nelson KE, Tsertsvadze T, del Rio C. 2006. Risk behaviors and HIV, hepatitis B, and hepatitis C seroprevalence among injection drug users in Georgia. *Drug Alcohol Dependence*. 82(Suppl 1):S35–S38.

Singer M, Li J, Duke M. 2003. *Drug Use Patterns and AIDS Risk in China*. Portland, Oregon: Society for Applied Anthropology.

Singh S, Crofts N. 1993. HIV infection among drug users in north-east Malaysia. *AIDS Care*. 5:273–281.

Small W, Kain S, Laliberte N, Schechter MT, O'Shaughnessy MV, Spittal PM. 2005. Incarceration, addiction and harm reduction: Inmates experience injecting drugs in prison. *Substance Use & Misuse* 40:831–843.

Sowell RL, Lowenstein A, Moneyham L, Demi A, Mizuno Y, Seals BF. 1997. Resources, stigma, and patterns of disclosure in rural women with HIV Infection. *Public Health Nursing*. 14(5):302–312.

Stachowiak JA, Tishkova FK, Strathdee SA, Stibich MA, Latypov A, Mogilnii V, Beyrer C. 2006. Marked ethnic differences in HIV prevalence and risk behaviors among injection drug users in Dushanbe, Tajikistan, 2004. *Drug and Alcohol Dependence*. 82(Suppl 1):S7–S14.

Stein MD, Solomon DA, Herman DS, Anderson BJ, Miller I. 2003. Depression severity and drug injection HIV risk behaviors. *American Journal of Psychiatry*. 160:1659–1662.

Stopka A. 2006. Editor's introduction to this special issue on syringe access and secondary syringe exchange: International perspectives and future directions. *Substance Use and Misuse*. 41:771–776.

Strang J, McCambridge J, Best D, Beswick T, Bearn J, Rees S, Gossop M. 2003. Loss of tolerance and overdose mortality after inpatient opiate detoxification: Follow up study. *British Medical Journal*. 326:9589–9960.

Strathdee S, Palepu A, Cornelisse P, Yip B, O'Shaughnessy M, Montaner J, Schechter M, Hogg R. 1998. Barriers to use of free antiretroviral therapy in injection drug users. *Journal of the American Medical Association*. 280:547–549.

Strathdee SA, Galai N, Safaiean M, Celentano DD, Vlahov D, Johnson L, Nelson KE. 2001. Sex differences in risk factors for HIV seroconversion among injection drug users: A 10-year perspective. *Archives of Internal Medicine*. 161(10):1281–1288.

Taussig J, Junge B, Burris S, Jones TS, Sterk CE. 2002. Individual and structural influences shaping pharmacists' decisions to sell syringes to injection drug users in Atlanta, Georgia. *Journal of the American Pharmaceutical Association*. 42(6 Suppl 2):S40–S45.

Thorpe L, Ouellet L, Hershow R, Bailey S, Williams I, Williamson J, Monterroso E, Garfein R. 2002. Risk of hepatitis C virus infection among young adult injection drug users who share injection equipment. *American Journal of Epidemiology*. 155(7):645–653.

Todd CS, Safi N, Strathdee SA. 2005. Drug use and harm reduction in Afghanistan. *Harm Reduction Journal*. 2:13.

UNAIDS (Joint United Nations Programme on HIV/AIDS). 2005. *HIV/AIDS Prevention, Treatment and Care Among Injecting Drug Users and in Prison.* Ministerial meeting on "Urgent Response to the HIV/AIDS Epidemics in the Commonwealth of Independent States," Moscow, March 31 to April 1, 2005. [Online]. Available: http://www.unodc.org/pdf/event_2005-03-31_prisons.pdf [accessed June 30, 2006].

UNAIDS. 2006. *2006 Report on the Global AIDS Epidemic: A UNAIDS 10th Anniversary Special Edition.* Geneva: UNAIDS.

UNODC (United Nations Office on Drugs and Crime). 2002. *Amphetamine Type Stimulants Threaten East Asia: East Asia Now Has the Most Serious ATS Problems in the World.* [Online]. Available: http://www.unodc.un.or.th/factsheet/ATSissuesplans310102.htm [accessed June 25, 2006].

UNODC. 2004. *Law Enforcement.* [Online]. Available: http://www.unodc.un.or.th/law/ [accessed June 30, 2006].

UNODC. 2005. *2005 World Drug Report.* Vienna, Austria: UNODC.

Urbina A, Jones K. 2004. Crystal methamphetamine, its analogues, and HIV infection: Medical and psychiatric aspects of a new epidemic. *Clinical Infectious Diseases.* 38(6): 890–894.

USAID, UNAIDS, WHO, UNICEF, and POLICY Project. 2004. *Coverage of Selected Services for HIV/AIDS Prevention, Care, and Support in Low- and Middle-Income Countries in 2003.* Washington, DC: Futures Group, POLICY Project.

Vickerman P, Hickman M, Rhodes T, Watts C. 2006. Model projections on the required coverage of syringe distribution to prevent HIV epidemics among injecting drug users. *Journal of Acquired Immune Deficiency Syndromes.* 42(3):355–361.

Voluntary HIV-1 Counseling and Testing Efficacy Study Group. 2000. Efficacy of voluntary HIV-1 counseling and testing in individuals and couples in Kenya, Tanzania, and Trinidad: A randomised trial. *Lancet.* 356(9224):103–112.

Wasserheit JN. 1992. Epidemiologic synergy: Interrelationships between human immunodeficiency virus infection and other sexually transmitted diseases. *Sexually Transmitted Diseases.* 19:61–77.

Watters JK, Estilo MJ, Clark GL, Lorvick J. 1994. Syringe and needle exchange as HIV/AIDS prevention for injection drug users. *Journal of the American Medical Association.* 271:115–120.

Wawer MJ, Sewankambo NK, Serwadda D, Quinn TC, Paxton LA, Kiwanuka N, et al. 1999. Control of sexually transmitted diseases for AIDS prevention in Uganda: A randomised community trial. *Lancet.* 353:525–535.

WHO (World Health Organization). 2003a. *HIV/AIDS in Asia and the Pacific Region.* Annual report. Manila, Philippines: WHO Western Pacific Regional Office.

WHO. 2003b. *WHO Collaborative Study on Substitution Therapy of Opioid Dependence and HIV/AIDS.* Geneva, Switzerland: WHO.

WHO. 2004a. *Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants: Guidelines on Care, Treatment and Support for Women Living with HIV/AIDS and Their Children in Resource-Constrained Settings.* Geneva, Switzerland, WHO.

WHO. 2004b. *Policy Brief: Reduction of HIV Transmission in Prisons.* Geneva, Switzerland: WHO.

WHO. 2004c. *Evidence for Action: Effectiveness of Community-Based Outreach in Preventing HIV/AIDS Among Injecting Drug Users.* Geneva, Switzerland: WHO.

WHO. 2005a. *Policy and Programming Guide for HIV/AIDS Prevention and Care Among Injecting Drug Users.* Geneva, Switzerland: WHO.

WHO. 2005b. *Evidence for Action: Effectiveness of Drug Dependence Treatment in Preventing HIV among Injecting Drug Users.* Geneva, Switzerland: WHO.

WHO. 2005c. *WHO Model List of Essential Medicine*. 14th edition. [Online]. Available: http://whqlibdoc.who.int/hq/2005/a87017_eng.pdf [accessed August 11, 2006].

WHO. 2005d. *Policy Brief: Antiretroviral Therapy and Injecting Drug Users*. Geneva, Switzerland: WHO.

WHO, UNODC, UNAIDS. 2004. *Substitution Maintenance Therapy in the Management of Opioid Dependence and HIV/AIDS Prevention: Position Paper*. Geneva, Switzerland: WHO.

Wood E, Kerr T, Small W, Jones J, Schechter M, Tyndall M. 2003. The impact of a police presence on access to needle exchange programs. *Journal of Acquired Immune Deficiency Syndromes*. 34(1):116–118.

Yu XF, Chen J, Scao Y, Beyrer C, Liu B, Wang Z, Liu W, Yang J, Liang S, Viscidi RP, Gu J, Gurrie-Glass, G, Lai S. 1999. Emerging HIV infections with distinct subtypes of HIV-1 infection among injection drug users from geographically separate locations in Guangxi Province, China. *Journal of Acquired Immune Deficiency Syndromes*. 22(2):180–188.

Zamani S, Kihara M, Gouya MM, Vazirian M, Nassirimanesh B, Ono-Kihara M, Ravari SM, Safaie A, Ichikawa S. 2006. High prevalence of HIV infection associated with incarceration among community-based injecting drug users in Tehran, Iran. *Journal of Acquired Immune Deficiency Syndromes*. 42(3):342–346.

Zhao M, Du J, Lu GH, Wang QU, Xu H, Zhu M, McCoy CB. 2006. HIV sexual risk behaviors among injection drug users in Shanghai. *Drug Alcohol Dependence*. 82(Suppl 1):S43–S47.

Zweben JE, Cohen JB, Christian D, Galloway GP, Salinardi M, Parent D, Iguchi M, Methamphetamine Treatment Project. 2004. Psychiatric symptoms in methamphetamine users. *American Journal of Addiction*. 13(2):181–190.

2

Treatment for Drug Dependence

The most effective way for IDUs to reduce their risk for contracting HIV through contaminated injecting equipment is to stop using drugs, and if that is not possible, to stop or reduce the frequency of injecting. Drug dependence treatment is therefore a critical HIV prevention strategy. It can interrupt HIV transmission by reducing drug-related HIV risk behavior, including frequency of drug use, injecting drug use, or sharing of injecting equipment. Although not the primary goal, drug treatment programs also have the potential to reduce risk behavior associated with the sexual transmission of HIV, such as sexual activity triggered by disinhibition or other drug effects, and engaging in sex in exchange for drugs or money. Beyond its effects on HIV transmission, drug dependence treatment can reduce other adverse health and social effects of drug abuse, including deaths from overdose and other drug-related causes of excess morbidity and mortality, and serve as an entry point into health and social services, including HIV/AIDS treatment (Sorenson and Copeland, 2000).

Drug dependence treatment can occur in a variety of settings, including inpatient, outpatient, and residential venues, and often blends different treatment approaches, including pharmacotherapy and psychosocial interventions. This chapter addresses the efficacy and effectiveness of pharmacotherapies—both agonist and antagonist agents for treating opioid[1] depen-

[1]"Opiates are a group of psychoactive substances derived from the poppy plant, that includes opium, morphine, codeine, and some others. The term 'opiate' is also used for the

dence, and pharmacotherapies for treating stimulant dependence (on cocaine or amphetamine-type drugs)—as well as psychosocial interventions. This chapter also examines the extent to which drug treatment provides IDUs with links to other health and social services.

The primary goal of drug abuse treatment is to reduce drug use. By doing so, it may also decrease injection drug use and other risk behaviors associated with drug use and provide a platform for providing other specific interventions directly targeting HIV transmission. Thus it may have direct, indirect, and facilitative effects on prevention of HIV transmission. As a result, the Committee first reviews the evidence regarding the effectiveness of drug treatment in reducing drug use and improving treatment-related outcomes, and then considers the impact of such treatment on HIV-related outcomes.

Efficacy refers to how well a treatment works under the best of circumstances, or in controlled clinical trials. Effectiveness refers to how well the treatment works in actual clinical practice. From a public health perspective, a particular treatment will have the greatest impact on HIV transmission if it is effective in reducing drug use and drug- and sex-related HIV risk behavior, and if it attracts and retains a large-enough proportion of drug-dependent individuals. Some treatments may be efficacious in controlled clinical trials but difficult to scale up for widespread, effective use in community settings. Other treatments may be efficacious but not attractive enough to patients to gain widespread acceptance. Although clinically efficacious treatments may reduce drug use and HIV transmission among drug-dependent patients who receive the treatment, unless these treatments are sufficiently widely disseminated, accessible, and attractive to the entire population of drug-dependent individuals, even the most efficacious treatment will not substantially reduce HIV transmission and other problems resulting from drug dependence in a country.

Social factors may also affect the willingness of drug-dependent patients to participate in efficacious treatments. Discrimination against patients receiving treatment for drug dependence and the stigma associated with drug dependence, as well as the monetary costs and other demands of treatment, can deter drug-dependent individuals from seeking or remaining

---

semisynthetic drug heroin that is produced from poppy compounds. The term 'opioids' refers to opiates and other semisynthetic and synthetic compounds with similar properties. Opioids are dependence producing substances, which elicit their effects by activating opioid receptors in the brain. Opioids are generally consumed by injection, oral ingestion or inhalation of the fumes produced by heating. Regular use of opioids can lead to opioid dependence" (WHO et al., 2004, p. 4).

in treatment (IOM, 1990). For drug abuse treatment to be most effective in reducing HIV transmission, it is essential that social policies encourage rather than discourage participation in treatment. In addition, consistent encouragement or even pressure to enter and remain in treatment from family members, friends, community leaders, or authorities can increase treatment engagement and contribute to successful treatment outcomes (IOM, 1990). The criminal justice system can also play an important role in getting drug users into treatment and outcomes by providing treatment as an alternative to incarceration, or as a condition of probation or parole (IOM, 1990).

THE COMMITTEE'S APPROACH TO EVALUATING THE STRENGTH OF THE EVIDENCE

A large number of systematic approaches to evaluating the quality and strength of scientific evidence are available. Many of these approaches, such as that used by the U.S. Preventive Services Task Force,[2] rely on explicit criteria to assign a "grade" to the evidence. Others use a more qualitative approach. In evaluating the strength of the evidence on the effectiveness of HIV prevention strategies for IDUs, the Committee used a structured qualitative method based on an approach developed by the GRADE Working Group—a collaboration of researchers that aims to address problems with rating systems (GRADE Working Group, 2004).

The GRADE approach takes into account strength of study design, study quality, consistency of findings across studies, directness/relevance of outcome measures, and populations. In establishing causality, this approach grades randomized trials as strong, prospective cohort and case-control studies as moderate, and other observational studies and reports as modest (e.g., serial cross-sectional, ecologic) or weak (e.g., cross-sectional) (see Box 2.1 for a description of common research study designs). The approach downgrades studies for serious limitations on quality; important inconsistencies; sparse, indirect, or imprecise data; low follow-up rates; and a high probability of reporting bias. Studies are upgraded for strong evidence of an association, consistency of effect, demonstration of dose-response, and good analytic control of confounders. Combining these elements, the approach assigns evidence to one of four quality categories:

- Strong: Further research is very unlikely to change confidence in the estimate of the effect.

[2]The task force's rating system for the strength of the evidence is available at: http://www.ahrq.gov/clinic/3rduspstf/ratings.htm.

- Moderate: Further research is likely to have an important impact on confidence in the estimate of effect, and may change the estimate.
- Modest: Further research is very likely to have an important impact on confidence in the estimate of effect, and likely to change the estimate.
- Weak: Further research is very likely to change the estimate, and possibly the direction of a very uncertain estimate of effect.

The Committee considered other factors when rating the strength of evidence regarding an intervention. These included the total number of studies, their generalizability, the intervention's applicability in practice, tradeoffs between benefits and harm, and acceptability to recipients. While considering all evidence as potentially policy relevant, the Committee sought to place greater weight on evidence of the highest quality in making its conclusions and recommendations.

EFFICACY AND EFFECTIVENESS OF PHARMACOTHERAPIES

This section first reviews evidence of effectiveness for opioid agonist therapies on (1) overall drug use and treatment-related outcomes; (2) drug-related HIV risk behavior; (3) sex-related HIV risk behavior; and (4) HIV incidence or seroconversion. The section considers factors that affect the impact of length of treatment, dosage, and adjunctive psychosocial therapy on the effectiveness of these treatments.

Opioid agonist medications have two primary clinical applications: they can be used on a limited basis to facilitate opioid detoxification,[3] or they can be administered over a longer-period as a maintenance treatment (IOM, 1995). This report focuses on the latter application. The section also reviews evidence of unintended consequences of opioid agonist therapy, such as misuse and diversion of treatment medications into illicit channels. The section then examines evidence on the effectiveness of opioid antago-

[3]Detoxification refers to medically supervised withdrawal from a substance until the person reaches a drug-free state. Pharmacological agents are often used during detoxification to alleviate client discomfort and to reduce potential complications. Opioid agonist medications can be used to help manage withdrawal symptoms during detoxification from opioids (IOM, 1990). When used to assist with detoxification, opioid agonist medications are provided tapered doses until the patient achieves a drug-free state (IOM, 1990, 1995). Detoxification alone is not considered an effective treatment (IOM, 1990). Studies show users have high rates of relapse to drug use when detoxification is not followed by further therapeutic intervention (IOM, 1990). Several other detoxification strategies can also be used including symptomatic treatment of withdrawal effects (e.g., with clonidine), or precipitated withdrawal without medication (IOM, 1995). This report does not address the relative advantages and disadvantages of these approaches.

BOX 2-1: Definitions of Common Research Study Designs

Randomized control trial (RCT): An epidemiologic experiment in which subjects in a population are randomly allocated into groups, usually called "study" and "control" groups, to receive or not to receive an experimental preventive or therapeutic procedure, maneuver, or intervention. The results are assessed by rigorous comparison of rates of disease, death, recovery, or other appropriate outcome in the study and control groups, respectively. RCTs are generally regarded as the most scientifically rigorous method of hypothesis testing available in epidemiology.

Case-control study: A study that starts with the identification of persons with the disease (or other outcome variable) of interest, and a suitable control (comparison, reference) group of persons without the disease. The relationship of an attribute to the disease is examined by comparing the diseased and non-diseased with regard to how frequently the attribute is present or, if quantitative, the levels of the attributes, in each of the groups.

Cohort study: The analytic method of epidemiologic study in which subsets of a defined population can be identified who are, have been, or in the future may be exposed or not exposed, or exposed in different degrees, to a factor or factors hypothesized to influence the probability of occurrence of a given disease or other outcome. The main feature of cohort study is observation of large numbers over a long period (commonly years) with comparison of incidence rates in groups that differ in exposure levels. The alternative terms for a cohort study, i.e., follow-up, longitudinal, and prospective study, describe an essential feature of the method, which is observation of the population for a sufficient number of person-years to generate reliable incidence or mortality rates in the population subsets. This generally implies study of a large population, study for a prolonged period (years), or both.

nist medication, which blocks the euphoric or rewarding effects of heroin or other opioids, and thus may help prevent resumption of opioid use. In addition, the Committee reviews the evidence of effectiveness for pharmacological treatments of stimulant dependence.

In reviewing pharmacological treatments for opioid and stimulant abuse, the Committee relied partly on several recent reviews and meta-analyses by the Cochrane Collaboration.[4] The Committee also relied partly

[4]The Cochrane Drugs and Alcohol Review Group is part of the Cochrane Collaboration, which was developed in the United Kingdom in 1992 with the goal of producing systematic reviews of the effects of various health care interventions that clinicians can use to guide their day-to-day practice. The review group conducts systematic reviews primarily of randomized clinical trials and controlled clinical trials of prevention, treatment, and rehabilitation interventions targeting drug dependence. The review group has published more than 30 reviews and 15 protocols. These are available at: http://alcalc.oxfordjournals.org/cgi/content/full/36/2/109; http://www.cochrane.org/newslett/DrugsandAlcoholAutumn2005.pdf.

Cross-sectional study: A study that examines the relationship between diseases (or other health-related characteristics) and other variables of interest as they exist in a defined population at one particular time. The presence or absence of disease and the presence or absence of the other variables (or, if they are quantitative, their level) are determined in each member of the study population or in a representative sample at one particular time. The relationship between a variable and the disease can be examined (1) in terms of the prevalence of disease in different population subgroups defined according to the presence or absence (or level) of the variables and (2) in terms of the presence or absence (or level) of the variables in the diseased vs. the non-diseased. Note that the disease prevalence rather than incidence is normally recorded in a cross-sectional study. The temporal sequence of cause and effect cannot necessarily be determined in a cross-sectional study.

Mathematical model: A representation of a system, process, or relationship in mathematical form in which equations are used to simulate the behavior of the system or process under study. The model usually consists of two parts: the mathematical structure itself, and the particular constants or parameters associated with them. A mathematical model is deterministic if the relations between the variables involved take on values not allowing for any play of chance. A model is said to be statistical, stochastic, or random, if random variation is allowed to enter the picture.

Ecological study: A study in which the units of analysis are populations or groups of people, rather than individuals. An ecological correlation is a correlation in which units studied are populations rather than individuals. Correlations found in this manner may not hold true for the individual members of these populations.

SOURCE: Verbatim definitions from A Dictionary of Epidemiology (Last, 1995).

on an earlier IOM report, *Treating Drug Problems* (1990). The Committee updated the search strategies used in the Cochrane reviews to identify critical studies published since those reviews occurred. (See Appendix B for more detail on the Committee's review methodology.)

OPIOID AGONIST MAINTENANCE PHARMACOTHERAPY

Opioid agonist maintenance therapies prevent withdrawal symptoms, decrease craving, and—by creating cross-tolerance to these effects—block or diminish the effects of illicit opioid use. Use of these long-acting oral medications allows patients to stabilize physiologically so that they can reengage in normal life activities (WHO et al., 2004; IOM, 1990). Due to their long half life and resulting steady state, opioid agonists are not intoxicating and do not impair function when used at clinically appropriate and stable doses over time (IOM, 1990, 1995). This is a central phenomenon that distinguishes their therapeutic use from their misuse when injected,

and distinguishes agonist treatment agents from other opioids, such as heroin, that are misused for their consciousness-altering properties.

Many studies have examined the efficacy and effectiveness of opioid agonist maintenance therapies for treating opioid dependence. The Committee limited its review of evidence to the two most commonly used opioid agonist therapies, methadone and buprenorphine. Other pharmacological agonist agents have been used in some countries for both detoxification and maintenance therapy. Although many studies have demonstrated Levo-Alpha-Acetyl-Methadol's (LAAM's) effectiveness (see Clark et al., 2002) as a maintenance therapy for treating opioid dependence, reports of serious cardiac-related adverse events led to its withdrawal from the European market in 2001 (EMEA, 2001) and to extensive labeling changes for U.S. package inserts (U.S. FDA, 2001).[5] Other opioid agonists, including prescription heroin (diacetylmorphine), tincture of opium, dihydrocodeine, and oral preparations of morphine, have been studied in limited settings but are not widely used (MacCoun and Reuter, 2001; WHO et al., 2004).

Effects on Drug Use and Treatment-Related Outcomes

A number of randomized clinical trials (RCTs) have shown the efficacy and effectiveness of methadone and buprenorphine maintenance therapies versus no opioid agonist treatment for drug and treatment-related outcomes. The evidence for each of these therapies is examined below.

Methadone

An extensive body of evidence spanning over three decades supports the efficacy of methadone maintenance as a treatment for opioid dependence. In a recent Cochrane review (Mattick et al., 2003a), investigators conducted a meta-analysis of six RCTs comparing methadone maintenance treatment (MMT) with either placebo maintenance or other non-pharmacological therapy for heroin dependence.[6] The six studies were conducted in diverse locations, including the United States, Sweden, Hong Kong, and Thailand. Two of the six trials were double-blinded and

[5]Roxanne Laboratories, Inc., the manufacturer of ORLAAM ® (Levomethadyl hydrocholoride acetate) Oral Solution, 10 mg/mL, CII, announced that it was discontinuing sale and distribution of its product after the current inventory was depleted (Roxanne Laboratories, Inc., 2003).

[6]Non-pharmacological control groups in the four non-placebo trials include those assigned to waitlist (Dole, 1969; Yancovitz, 1991), drug-free rehabilitation (Gunne and Gronbladh, 1981), or methadone detoxification (Vanichseni, 1991).

placebo-controlled (Newman and Whitehill, 1979; Strain et al., 1993). The overall methodological quality of the studies was good. The procedures for ensuring that researchers and participants remained unaware of the randomization assignments were inadequate in one study (Dole et al., 1969), not adequately described in four studies (Gunne and Gronbladh, 1981; Newman and Whitehill, 1979; Strain et al, 1993; Vanichseni et al., 1991), and good in another (Yancovitz, 1991). Sample sizes were sometimes small, with two studies enrolling only 32 and 34 participants (Dole et al., 1969; Gunne and Gronbladh, 1981). Sample sizes for the four remaining studies ranged from 100 to 301 patients. Dosage was considered adequate in all studies.

The Cochrane meta-analysis examined the impact of treatment on treatment retention, opioid drug use as measured by self-reports and urine analyses, criminal activity, and mortality. The meta-analysis showed that MMT was more effective than placebo and non-pharmacological treatments in retaining patients in treatment (3 RCTs; relative risk [RR]=3.05; 95% confidence interval [CI]: 1.75–5.35), and in reducing heroin use (3 RCTs; RR=0.32; 95% CI: 0.23–0.44). The review found a positive—although not statistically significant—effect on reducing criminal activity (3 RCTs' RR=0.39; 95% CI: 0.12–1.25) and mortality (3 studies, 435 patients; RR=0.49; 95% CI: 0.06–4.23).

One RCT of MMT (Schwartz et al., 2006), published since the Cochrane review, supported these findings. The study randomly assigned a total of 319 participants on a 3:2 basis to interim methadone maintenance (with an individually determined dose and no regularly scheduled drug counseling) for 120 days (n=199), or a waiting list for community-based methadone treatment (n=120). Some 76 percent of those assigned to the interim methadone maintenance treatment entered comprehensive methadone treatment within 4 months, compared with some 21 percent ($p<0.001$) assigned to the waiting list. Interim methadone participants also reported significantly fewer days of heroin use ($p<0.001$), and had significantly fewer heroin-positive urine tests (<0.001). Self-reported crime was also significantly lower in the treatment. The finding that MMT reduces heroin use is consistent with the findings of the Cochrane review.

While RCTs have shown that MMT reduces heroin use and improves treatment retention, findings also suggest a positive effect of MMT on criminal behavior. As noted, the 2003 Cochrane review (Mattick et al., 2003a) found a positive but non-significant association between MMT and reductions in crime. Two quasi-experimental studies examining the effects of MMT program closures in California (Anglin et al., 1989; McGlothin and Anglin, 1981) found that MMT patients who were unable or unwilling to transfer to a private MMT program after a publicly funded MMT program was closed had higher rates of illicit drug use, arrest, and incarcera-

tion than patients in other locations who continued to receive MMT. Another study that followed a sample of opioid-dependent men enrolled in MMT found—when comparing pre- and post-admission periods—that retention in methadone treatment had a small but significant effect on criminal activity (Rothbard et al., 1999). Although these studies suggest that MMT has a positive impact on reducing crime, the results must be interpreted with caution because of the strong possibility of selection bias. That is, patients who enrolled in treatment might have reduced their criminal activity in any event, while patients who did not enroll might not have reduced their criminal activity even with treatment.

A number of studies have examined the impact of methadone treatment on mortality. As noted, the Cochrane review (Mattick et al., 2003a) on effectiveness of methadone maintenance found a trend suggesting that methadone had a protective effect on mortality, but it was not significant. Other non-experimental studies point to a reduction in mortality rates among people receiving opioid agonist treatment compared to out-of-treatment IDUs. For example, in a cohort study by Caplehorn et al. (1994), individuals who had left methadone maintenance treatment were three times more likely to die than those who were in treatment. Three studies by Fugelstad and colleagues (1995, 1997, 1998) found nearly all deaths of patients on methadone maintenance were due to disease already present prior to their entry to treatment (e.g., HIV), whereas the majority of heroin addicts out of treatment died as a result of overdose or violence. The significant limitation of non-experimental studies such as these is that self-selection bias could contribute to the findings of decreased mortality among people in treatment.

Buprenorphine

Another Cochrane review (Mattick et al., 2003b) examined the effectiveness of buprenorphine maintenance therapy vs. placebo or methadone maintenance therapy in retaining patients in treatment and reducing illicit drug use. The review considered 13 RCTs that met the inclusion criteria. All but one of the studies were double-blind, but only two were placebo-controlled (Johnson et al., 1995; Ling et al., 1998); most of the evidence came from comparing buprenorphine and methadone at varying dosage levels. The reviewers found that the methodological quality of the studies was high, except that 11 inadequately described how they concealed the allocation of treatment.

The authors found that high-dose buprenorphine maintenance was more efficacious than placebo and low-dose methadone in retaining individuals in treatment and reducing heroin use. However, high-dose buprenorphine had no advantage over high-dose methadone in retaining

patients, and was less efficacious than high-dose methadone in reducing heroin use.

Three RCTs of buprenorphine have been published since the 2003 Cochrane review, and their findings are consistent with that review. The first trial (Fudala et al., 2003) tested the efficacy and safety of buprenorphine and combined buprenorphine-naloxone[7] treatment in a U.S. office-based setting. In this multicenter, randomized, placebo-controlled trial, 323 opioid-dependent individuals received one of three treatments: (1) sublingual buprenorphine (16 milligrams) with naloxone (4 milligrams) (n=109); buprenorphine alone (16 milligrams) (n=105); or daily placebo for 4 weeks (n=109). The primary outcome measures were opioid-negative urine samples and patients' self-reported craving for opiates.

The researchers ended the placebo arm of the trial early because both the mono-buprenorphine tablet and the combination buprenorphine-naloxone tablet were more efficacious than placebo. The active treatment groups had higher percentages of opiate-free urine samples (17.8 percent for combined treatment and 20.7 percent for buprenorphine treatment) than the placebo group (5.8 percent; $p<0.0001$ for both comparisons). The active treatment groups also reported less craving for opiates than the placebo group. The later phase of the study showed that treatment was safe and well tolerated.

The second study was a randomized, double-blind, placebo-controlled trial in Norway (Krook et al., 2002). This 12-week study compared interim buprenorphine maintenance treatment versus placebo in patients on a waitlist for medication-assisted rehabilitation. Participants did not receive any psychosocial treatment as part of the study. Of 106 participants, 55 were randomized to receive a daily dose of 16 milligrams of buprenorphine, and 51 to placebo. Outcome measures included treatment retention, treatment compliance, self-reported drug abuse, well-being, and mental health status.

The average number of days in treatment was higher for the buprenorphine group (42 days) than the placebo group (14 days; $p<0.0001$). However, the attrition rate was significant for both groups, with 16 participants remaining in the buprenorphine group and 1 in the placebo group after 12 weeks. The authors attribute the retention problem to the lack of psychosocial support. The buprenorphine group also showed a larger drop in self-reported opioid use ($p<0.001$) and other drug and alcohol use ($p<0.01$), and a stronger increase in reported well-being ($p<0.01$) and life

[7]Naloxone is an opioid antagonist similar to naltrexone. Naloxone was included to reduce or prevent potential diversion or misuse of buprenorphine by injection.

satisfaction ($p<0.05$). Although these findings are consistent with those of other trials, this trial did not use urine toxicology screening to verify self-reported drug use.

The third study (Kakko et al., 2003) was a randomized, placebo-controlled trial conducted in Sweden to assess the 1-year efficacy of buprenorphine combined with psychosocial therapy in treating heroin dependence. Subjects included 40 individuals who had been dependent on heroin for at least 1 year (all but one injected heroin), but who were not eligible for methadone maintenance treatment. (In Sweden at the time of the trial, individuals were eligible only after 4 years of multiple daily heroin use and more than three unsuccessful attempts at drug-free treatment.) Participants were randomly assigned (1:1) to daily buprenorphine (16 milligrams per day for 12 months, with supervised administration for 6 months and possible take-home doses after that), or to a tapered buprenorphine regimen for 6 days followed by placebo. As part of a relapse-prevention program, all patients received cognitive-behavioral group therapy and weekly individual counseling. Participants submitted urine samples for testing for illicit opiates, stimulants, cannabinoids, and benzodiazepines. The primary outcome measure was retention in treatment for 1 year.

Results from Kakko et al. (2003) showed 75 percent treatment retention in the buprenorphine treatment group and 0 percent in the placebo group ($p=0.0001$; risk ratio: 58.7; 95% CI: 7.4–467.4). The authors attribute the high attrition rate in part to criteria that required involuntary dismissal from treatment for anyone who continued using illicit drugs. All 20 patients in the placebo group had urine tests that were positive for illicit drug use, and none remained in treatment beyond 2 months. In the buprenorphine group, four were involuntarily discharged for positive urine toxicology tests, and one voluntarily dropped out of treatment. The authors also note that withdrawal symptoms and perceived lack of suppression of craving among participants in the placebo arm could have contributed to illicit drug use and dropout. Urine samples in the buprenorphine group were 74.8 percent (standard deviation 59.6 percent) negative, on average, for substances analyzed. Mortality was substantially higher in the control group: four people (20 percent) died in the control group, and none in the buprenorphine group. The authors conclude that buprenorphine combined with psychosocial treatment is highly efficacious and safe.

Based on this evidence, the Committee concludes:

Conclusion 2-1: Strong and consistent evidence from well-designed, randomized, controlled trials (some double-blind, placebo-controlled) shows that opioid agonist maintenance treatment—including methadone and buprenorphine—is more effec-

tive than placebo and non-pharmacological treatment in reducing illicit opioid use and increasing retention in drug-abuse treatment for opioid-dependent patients. When available and accessible, opioid agonist maintenance treatment attracts and retains in treatment a large proportion of opioid dependent patients and thus can have a substantial public health benefit in the population.

Conclusion 2-2: Moderate evidence from randomized controlled trials and quasi-experimental studies suggest that opioid agonist maintenance therapy is associated with reductions in criminal behavior. Modest evidence from studies suggest that agonist maintenance therapy lowers mortality risk for those who remain in treatment, but the possibility of self-selection bias cannot be excluded.

Effects on Non-Opioid Drug Use

Concomitant abuse of other drugs is a common problem for opioid-dependent individuals, including patients on methadone and buprenorphine maintenance treatment. Co-occurring drug use among opioid-dependent people can increase rates of morbidity and mortality and undermine the effectiveness of opioid addiction treatment (Backmund et al., 2003; Leri et al., 2003).

Cocaine use, in particular, is prevalent among opioid-dependent people. The estimated prevalence of cocaine use among heroin-dependent people not in treatment ranges from 30 to 80 percent (Haisin et al., 1988; Schottenfeld et al., 1993; Schutz et al., 1994; Frank and Galea, 1996; Grella et al., 1995, 1997 as cited in Leri et al., 2003). Studies have also found high rates of chronic or intermittent cocaine use among patients enrolled in methadone programs (Kosten et al., 1987, 1988; Magura et al., 1998; cited in Leri et al., 2003). The effects of co-occurring cocaine use are particularly serious (Leri et al., 2003). Cocaine is most often injected in this population, and because of its short half life, can be injected more often, producing more opportunities for syringe sharing and a higher risk of HIV infection and other infectious diseases (Leri et al., 2003). Furthermore, opioid addicts who use cocaine are also more likely to have poor treatment outcomes, such as high dropout rates, involuntary dismissal from treatment, and high rates of relapse (Leri et al., 2003).

Concomitant use of alcohol, benzodiazepines, barbiturate, cannabis, and other drugs among opioid-dependent populations is also prevalent (Fairbank et al., 1993; Darke et al., 1995; Rooney et al., 1999; Hser et al., 2001; Backmund et al., 2003). Use of these drugs is also concerning. For instance, consumption of opioids and psychotropic substances with

respirant-depressive effects, such as alcohol, benzodiazepines, barbiturates, can lead to overdoses that are sometimes fatal (Backmund et al., 2003).

Because opioid agonist treatment is not pharmacologically specific to non-opioid drugs, we would not expect to see an impact on adjunctive drug use without additional intervention. While some studies have examined whether opioid agonist maintenance therapy is associated with changes in patterns of stimulant or other drug use, many of these studies had limitations that made it difficult to interpret or generalize their results, such as cross-sectional design, short time period, reliance on self-reported data, small sample size, or a single study site (Magura et al., 1998). No recent reviews have examined whether opioid agonist treatment is associated with changes in patterns of stimulants or other drug use.

Nevertheless, understanding patterns of concomitant drug use among opioid-dependent people—including those enrolled in opioid agonist treatment—is important to understanding HIV-related risks and in designing appropriate interventions for these populations. As discussed later in this chapter, the addition of certain behavioral interventions to opioid agonist maintenance therapy has been effective in reducing overall drug use for patients who are co-dependent on stimulants and opioids.

Effects on HIV Risk Behavior and Seroconversion

Opioid agonist treatment may reduce the risk of HIV infection in several ways. By reducing the use of opioids, such treatment may also reduce how often individuals inject, and also how often they share injecting equipment. These impacts depend partly on whether individuals are using opioids only or also using other drugs that may be injected, such as cocaine and amphetamine-type stimulants. Agonist treatment may also reduce the need to engage in high-risk behavior, such as exchanging sex for money or drugs. Such treatment may further connect users of illicit drugs with health and social services, and make them more receptive to prevention messages (Gowing et al., 2004).

A recent Cochrane review (Gowing et al., 2004; summary in Gowing et al., 2005) examined the effects of opioid agonist treatments on drug-related and sex-related HIV risk behavior and HIV seroconversion. The authors identified 28 studies of methadone treatment that met the criteria for inclusion: these studies specifically examined HIV risk behavior or incidence in relation to opioid agonist treatment, and the study authors described the treatment regimen adequately.

Of the 28 studies, 2 were randomized controlled studies (Dolan et al., 2003; Sees et al. 2000), 3 were prospective cohorts (Kwiatkowski and Booth, 2001; Maddux and Desmond, 1997; Metzger et al., 1993), and 2 were case controls (Moss et al., 1994; Serpellini and Carrieri, 1994). The

remaining studies were classified as "other descriptive studies."[8] Because the methodologies of the studies varied, the authors limited their analysis to a descriptive review that compared outcomes of the studies. In its own review, the Committee gave the most weight to evidence from the 7 studies with the strongest study designs, including controlled clinical trials, prospective cohorts, and case-control studies.

Drug-Related HIV Risk Behavior

Frequency of injecting: Six of the 28 studies provided the proportion of participants reporting injecting drug use before and after methadone treatment.[9] Eight studies offered data on the reported frequency of injection at baseline and follow-up,[10] and 2 studies[11] examined both the proportion and frequency of injection. One study was an RCT (Dolan et al., 2003), while the others were classified as descriptive. The studies varied in design, follow-up period, and method of reporting the frequency of injecting (such as frequency score, actual number of injections, and days of injecting use). However, they all showed statistically significant decrease in injecting behavior from baseline to follow-up—periods that ranged from 3 to 12 months (Gowing et al., 2004, 2005).

In the one RCT (Dolan et al., 2003), investigators studied whether MMT reduced heroin use and syringe sharing among opiate-dependent individuals in an Australian prison system from 1997 to 1998. Of 593 eligible prisoners seeking drug treatment, 382 were randomly assigned to MMT (30 milligrams per day initially, increased up to 60 milligrams) (n=191), or a waitlist control group (n=191). Researchers used toxicology tests of hair samples and self-reports to measure heroin use, and self-reports to measure drugs used and the frequency of injection and syringe sharing. Study subjects were interviewed at baseline and about 4 months later. At follow-up, 129 (68 percent) of the MMT group and 124 (65 percent) of the control group who had been in continuous custody were reinterviewed. Participants in the MMT group had significantly lower levels ($p<0.001$) of

[8]If a controlled clinical trial collected data on HIV seroprevalence and risk behavior for secondary analysis (such as during a study primarily designed to test the efficacy of methadone versus buprenorphine on drug use), the Cochrane reviewers regarded these data as being derived from a descriptive study (Gowing et al., 2004).

[9]RCT (Dolan et al., 2003); descriptive studies (Camacho et al., 1996; Chatham et al., 1999; Gossop et al., 2000; King et al., 2000; Magura et al., 1991).

[10]RCT (Dolan et al., 2003); descriptive studies (Batki et al., 1989; Brooner et al., 1998; Camacho et al., 1996; Chatham et al., 1999; Kwiatkowski and Booth, 2001; Simpson et al., 1995; Strang et al., 2000).

[11]Descriptive studies (Camacho et al., 1996; Chatham et al., 1999).

self-reported drug injection than controls in each of the three months before the follow-up interview. The treatment and control groups did not show significant differences in heroin use as measured by nanograms in hair, but the hair tests are not sensitive to differences in frequency of heroin use, so the lack of significant differences does not necessarily contradict the validity of the findings based on self-report.

Sharing of injecting equipment: Seven studies examined the proportion of participants who reported sharing injecting equipment before and after a period of MMT. Six of seven studies[12] found a significant reduction in sharing between baseline and follow-up periods. The seventh study (King et al., 2000) found a non-significant reduction in reported syringe sharing (risk ratio 0.54; 95% CI: 0.23–1.27) (Gowing et al., 2004, 2005).

Four studies (Dolan et al., 2003; Metzger et al., 1993; Stark et al., 1996; Thiede et al., 2000) also provided data on sharing of injecting equipment among those who received MMT compared with those who received no methadone or only limited doses. In three studies (Dolan et al., 2003; Metzger et al., 1993; Stark et al., 1996), those receiving MMT were significantly less likely to report sharing injecting equipment. In the study with the strongest design, the RCT by Dolan et al. (2003), treated subjects had lower reported levels of syringe sharing at follow-up than controls (20 percent vs. 54 percent, $p<0.001$) (Gowing et al., 2004, 2005).

Drug-related risk scores: Four studies provided data on drug-related HIV risk scores before and after MMT.[13] Three of the four studies (Abbott et al., 1998; Avants et al., 1998; Chatham et al., 1999) found significant decreases in drug-related HIV risk behavior before and after MMT. The fourth study (Sees et al., 2000), an RCT, found a non-significant reduction in mean risk scores between intake and the 6-month follow-up for both the MMT and 180-day methadone detoxification groups (Gowing et al., 2004, 2005).

A final study (Baker et al., 1995) compared drug risk scores for cohorts of IDUs who currently, previously, or never received MMT. The study found a significant reduction in risk-related scores for the group receiving MMT, compared with the latter two groups combined (the proxy for not in methadone treatment) (Gowing et al., 2004, 2005).

---

[12]RCT (Dolan et al., 2003); descriptive studies (Camacho et al., 1996; Chatham et al., 1999; Gossop et al., 2000; King et al., 2000; Grella et al., 1996; Margolin et al., 2003).

[13]These studies used rating scales such as the Risk Assessment Battery and the HIV Risk Taking Behavior Scale to derive both drug-related and sex-related HIV risk scores and an overall HIV risk score (Gowing et al., 2004, 2005). This section focuses on drug scores.

Based on this evidence, the Committee concludes:

Conclusion 2-3: Moderate to strong evidence from one RCT and a number of observational studies shows that patients receiving methadone maintenance treatment report reductions in several drug-related HIV risk behaviors, including frequency of injecting and sharing of injecting equipment. These patients also had lower summary scores of drug-related risk behavior compared with pre-treatment levels.

Sex-Related HIV Risk Behavior

Because opioid agonist maintenance therapy is not designed to reduce sexual risk behavior, one would not expect to see an impact on such behavior use without additional intervention. However, the Cochrane review identified a number of observational studies that have examined the impact of MMT on sex-related risk behavior, including multiple sex partners, exchange of sex for drugs or money, and unprotected sex (Gowing et al., 2004, 2005).

Multiple sex partners and commercial sex: Four studies—classified as descriptive by Cochrane—provided data on the proportion of participants reporting multiple sex partners or exchanges of sex for drugs or money. In three of these studies (Camacho et al., 1996; Chatham et al., 1999; Grella et al., 1996), participants reported significantly fewer multiple partners or exchanges of sex for drugs or money after MMT than before treatment. In King et al. (2000), relatively few participants reported such behavior before or after MMT (Gowing et al., 2004, 2005).

Two studies reported on sex-related risk behavior among cohorts of IDUs either receiving or not receiving methadone treatment. In a prospective cohort study by Metzger et al. (1993), significantly more participants in the out-of-treatment cohort reported commercial transactions for sex in the 6 months before baseline than participants in the methadone treatment cohort (46 percent vs. 28 percent; $p<0.01$). The out-of-treatment group also reported a higher average number of sex partners (4.6 versus 2.3; $p<0.01$) during the same period.

In a cross-sectional study by Meandzija et al. (1994), participants in the methadone treatment cohort reported fewer sex partners in the past 30 days than out-of-treatment injection drug users, although the result was not statistically significant. The in-treatment cohort also reported a significantly lower frequency of exchanging sex for money or drugs during the past 30 days, compared with the out-of-treatment cohort (Meandzija 1994; Gowing et al., 2004, 2005). The Cochrane review (Gowing et al., 2004)

identified a third cohort study (Britton, 1994) that found differences in the number of sex partners between cohorts of drug users continuing in or stopping methadone. However, the review gave little weight to the findings because of the significant differences between the groups at baseline (Gowing et al., 2004, 2005).

Unprotected sex: The measure for assessing exposure to unprotected sex varied substantially across studies included in the Cochrane review. Six of the studies[14] defined such exposure as the use of condoms in half or fewer sexual encounters. Four of these studies (Camacho et al., 1996; Chatham et al., 1999; Gossop et al., 2000; Margolin et al., 2003) found statistically significant reported reductions in unprotected sex, while two did not. In Grella et al. (1996), fewer participants reported unprotected sex at follow-up compared with baseline, but the finding was not significant. In King et al. (2000), the number of participants reporting unprotected sex actually rose slightly after treatment, but the finding was not significant.

Three studies compared condom use among groups of IDUs in or out of methadone treatment. One cohort study (Metzger et al., 1993) and one cross-sectional survey (Meandzija et al., 1994) found no significant differences in reported condom use between in-treatment and out-of-treatment groups. A third cohort study (Stark et al., 1996) found non-significant drops in reported condom use in the methadone treatment cohort compared with the out-of-treatment cohort (Gowing et al., 2004, 2005).

Sex-related risk: Four studies reported on sex-related risk scores. Two (Abbott et al., 1998; Avants et al., 1999) reported a significant reduction in sex-related risk from baseline to 6-month follow-up. A randomized controlled trial (Sees et al., 2000) found a reduction in sex-related scores, but it was not significant. A final study (Baker et al., 1995) found no difference in sex-related risk scores for IDUs in methadone treatment compared with IDUs who were previously in treatment or had no prior history of MMT (Gowing et al., 2004, 2005).

Based on this evidence, the Committee concludes:

> ***Conclusion 2-4: Because opioid agonist maintenance therapy is not designed to reduce sex-related risk behavior, one would not expect to see a substantial impact on such behavior without additional intervention. Indeed, evidence from observational studies is***

[14]Descriptive studies: Camacho et al. (1996); Chatham et al. (1999); Gossop et al. (2000); Margolin et al. (2003); Grella et al. (1996); King et al. (2000).

weak and inconclusive on whether opioid agonist therapy alone is associated with reductions in high-risk sexual behavior. Some studies suggest that MMT is associated with small reductions—compared with pre-treatment baseline measures—in the number of sexual partners and exchanges of sex for money or drugs, but that it has virtually no effect on reported rates of unprotected sex.

HIV Seroconversion

Four studies in the 2004 Cochrane review specifically examined the impact of MMT on HIV seroconversion (Gowing et al., 2004, 2005). In a prospective cohort study, Metzger et al. (1993) followed 152 people in methadone treatment and 103 out-of-treatment opiate users in Philadelphia for 18 months. At baseline, the HIV seroprevalence rate was 10 percent for the in-treatment group and 16 percent for the out-of-treatment group. A follow-up study of HIV-negative participants over the next 18 months found a six-fold difference in seroconversion rates among those in treatment (3.5 percent) and out of treatment (22 percent). Of the participants, 46 percent (n=85) were in treatment during the entire 18-month period, 24 percent (n=45) attended treatment intermittently, and 30 percent (n=55) were not in treatment at any point. The odds of seroconversion were 7.63 among untreated subjects (95% CI: 1.99–29.27; $p<0.01$) and 1.08 (not significant) among intermittent-treatment subjects compared with subjects in continuous MMT. Untreated subjects were thus seven times more likely to seroconvert during the 18-month period than individuals who remained in treatment. These findings persisted in analysis controlling for confounders, although the possibility of self-selection bias exists.

Moss et al. (1994) followed a cohort of IDUs entering MMT or detoxification in San Francisco from 1985 to 1990. In a subsample of 681 who were HIV-negative at first visit and seen at least twice, 22 seroconverted. Using a case-control design and stratifying the sample by time spent in methadone treatment, the authors found that 11 of 145 (7.6 percent) who spent less than 12 months in treatment seroconverted, compared with 11 of 536 (2.1 percent) who spent more than 12 months in treatment (adjusted hazard ratio 4.0; $p=0.002$). A history of 1 or more years in methadone maintenance (per lifetime) was therefore a highly protective factor against HIV seroconversion. This effect persisted, in both men and women, after adjustment for race and other confounding factors. Nonetheless, the possibility of selection bias could not be ruled out.

Serpellini and Carrieri (1994) conducted a nested case-control study of seroconverters (cases) who were part of a cohort of 952 HIV-negative IDUs (controls) followed from 1985 to 1991, to assess the impact of MMT on HIV infection. The study included 40 cases and 40 controls. Controls were

matched with cases on sex, age, duration of drug use, and follow-up time. In multivariate analyses, lower daily dose and more time out of methadone treatment were associated with higher HIV seroconversion. Time spent in methadone treatment was the major determinant of remaining HIV-free; the model showed that the risk of becoming HIV infected increased 1.5 times for every 3 months (of the last 12) spent out of methadone treatment. The authors similarly found a significant inverse relationship between average daily methadone dose and HIV seroconversion.

Williams et al. (1992) conducted a follow-up study of a cohort of MMT clients in New Haven with a history of injecting drug use. The study followed 98 IDUs who were HIV-seronegative at baseline and who completed at least one follow-up visit for a mean of 39 months. Nine participants seroconverted during the follow-up period, and 89 remained seronegative. Stratified by time in treatment, subjects who remained on methadone treatment without interruption during the follow-up period were less likely to seroconvert than those in the interrupted-treatment group. One participant of the 56 in the continuous-treatment group seroconverted, compared with 8 of the 42 in the interrupted-treatment group (odds ratio [OR]=12.9; 95% CI: 1.6–584, p=0.0045). Because the follow-up period varied by group (averaging 29 months in the continuous-treatment group versus 53 months in the interrupted-treatment group), the seroconversion rate per person-year was computed for each group. The HIV-1 seroconversion rate was 0.7 per 100 person-years (95% CI: 0.1–5.3) for the continuous-treatment group, and 4.3 per 100 person-years (95% CI: 2.2–8.6) for the interrupted-treatment group. The difference between seroconversion rates in the two groups was not significant (Z=1.65; p=.10; two-sided). Continuous methadone treatment had a non-significant association with lower HIV seroconversion. However, the small sample size and the risk of selection bias arising from loss to follow-up are important limitations of this analysis.

Based on this evidence, the Committee concludes:

> ***Conclusion 2-5: 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 sero-conversion is inversely related to the length of time in treatment. However, the possibility of bias in these findings from self-selection cannot be ruled out: that is, patients who resist treatment or engage in risky behaviors may leave treatment, while patients with fewer HIV risk behaviors may stay in treatment longer.***

Conclusion 2-6: Evidence regarding the effects of agonist maintenance therapy on HIV-related risk behavior and HIV seroconversion is based on studies of methadone conducted in developed countries. Other studies (reviewed in the previous section) found that buprenorphine has comparable efficacy in reducing dependence on illicit opioids. Nothing in the literature contradicts the logic that buprenorphine would exert an effect on HIV risk behavior and incidence comparable to that of methadone treatment. Nor does the literature suggest that the effectiveness of opioid agonist maintenance treatment would be diminished in developing countries.

Factors Affecting Outcomes of Opioid Agonist Treatment

As noted, studies have shown that opioid agonist treatment reduces illicit opioid use, improves retention in treatment, and reduces drug-related HIV risk behavior and incidence. Three major clinical factors that increase the likelihood of these positive outcomes are appropriate length of treatment, adequate dosage, and provision of psychosocial treatments along with maintenance medications.

Length of Treatment

The Committee identified four randomized controlled trials that compared methadone maintenance treatment with methadone-assisted detoxification. In all cases, maintenance treatment was found to be superior to detoxification in terms of treatment retention and heroin use. In the first RCT (Sees et al., 2000), investigators compared outcomes for opiate-dependent patients on MMT versus long-term (180-day) methadone-assisted detoxification. Results showed that patients in the MMT arm had improved treatment retention and lower heroin use than the detoxification group. Dropout rates were significantly higher in the detoxification arm than in the MMT arm. Drug-related HIV risk behavior, but not sex-related risk behavior, also declined more in the MMT group.

A second RCT conducted in Thailand found that patients assigned to MMT had greater likelihood of completing treatment and were less likely to use heroin than those assigned to a short-term (45-day) methadone detoxification arm (Vanichseni et al., 1991). A third RCT by Newman and Whitehill (1979) conducted in Hong Kong found that the MMT group had greater treatment retention than the control group, which was detoxified (dose of methadone was decreased by 1 milligram per day) and then maintained on placebo. At the end of 32 weeks, only 10 percent of the controls were still in treatment, compared with 76 percent of the MMT

group. At the end of 3 years, only 1 of the original 50 patients assigned to detoxification/placebo was still in treatment, while 56 percent of MMT patients remained in treatment.

Finally, Strain et al. (1993) found that patients on active maintenance therapy had higher treatment retention rates than those who entered a 35-day detoxification period and then remained on placebo. Illicit opiate use was also lower among patients on 50 milligrams of methadone per day, compared with those receiving 20 or 0 milligrams per day. In addition, as noted above, quasi-experimental studies examining the effects of program closures in California found higher rates of illicit drug use, arrest, and incarceration among those whose MMT was terminated (even after prolonged MMT) than among comparison samples in other locations who continued to receive MMT during the same period (Anglin et al., 1989; McGlothin and Anglin, 1981).

Based on this evidence, the Committee concludes:

> ***Conclusion 2-7: Strong evidence from several large, randomized clinical trials shows that continuous agonist maintenance therapy is associated with longer treatment retention—and reductions in illicit opioid use and relapse to opioid dependence—than short-term use of these agents. Furthermore, modest evidence from quasi-experimental studies also suggests that discontinuation of agonist maintenance therapy is associated with higher rates of readdiction and criminal behavior. Agonist maintenance therapies are effective while they are provided, and no evidence suggests a benefit to early termination. Thus, reasonable clinical guidance is to continue such therapies as long as they are associated with positive effects.***

Dosage

Regulations and clinical practice standards for long-term opioid maintenance therapy vary widely (Faggiano et al., 2003). However, strong evidence from a variety of sources shows that methadone maintenance is a dose-dependent treatment; that is higher doses of opioid agonist therapies are more efficacious than moderate and lower doses in managing opioid dependence.

In a recent Cochrane review (Faggiano et al., 2003), the authors examined results from 21 studies (10 randomized controlled trials and 11 controlled prospective studies), to compare the effectiveness of MMT at different doses. The results of this review support the conclusion that high dosages of 60–100 milligrams per day of methadone are more effective than low doses (1–39 milligrams per day) and moderate doses (40–59 milligrams per

day) in retaining patients in treatment and reducing the use of heroin during treatment. A study by Strain and colleagues (1999) also illustrates that benefits increase with higher doses. An RCT comparing the clinical efficacy of moderate-dose (40–50 milligrams per day) vs. high-dose (80–100 milligrams per day) methadone maintenance found that while both groups decreased their illicit opioid use, the high-dose methadone group had significantly greater decreases.

Although high doses show the greatest benefits, low-dose or "low-threshold" methadone programs have been used in some places, notably in Amsterdam, to encourage more opiate-dependent people to enter treatment. The Amsterdam programs made methadone easily accessible (e.g., through use of mobile vans, absence of waiting lists) and acceptable to users (e.g., by allowing participation regardless of illicit drug use, offering services in a supportive way, and making it easy to enter or leave the program) (van Ameijden et al., 1999). The goal of the program was to stabilize drug users by preventing withdrawal symptoms in the hopes that they will gradually move toward more intensive treatment for drug dependence (Hartgers et al., 1992). The low-threshold programs in Amsterdam succeeded in bringing 60–70 percent of heroin-dependent individuals into methadone treatment (Termorshuizen et al., 2005). One follow-up study of the programs found, however, that low-threshold programs did not provide any protective effect against HIV seroconversion (Hartgers et al., 1992). Length of time participating in the low threshold program was positively correlated with HIV infection; that is, long-term participants had a higher prevalence of HIV infection than short-term or irregular participants (Hartgers et al., 1992). While there are many confounders to this study, the study provides no evidence that the low-dose programs decrease HIV transmission risk.

While fewer studies compare higher and lower doses of buprenorphine, dose-ranging studies show dose-dependent effects of buprenorphine on heroin use in heroin-dependent patients. Animal and human laboratory studies also show dose-dependent effects of buprenorphine on heroin self-administration. Some randomized controlled trials show greater reductions in illicit opioid use associated with higher daily doses of buprenorphine (12–16 milligrams), compared with lower doses (2–4 milligrams) (Ling et al., 1998; Johnson et al., 1995; Schottenfeld et al., 1993, 1997).

The optimal doses for individuals are the joint decision of clinicians and patients. However, clinicians, policymakers, and regulators should consider the strong dose-response effects of opioid agonist therapies when developing guidelines, and avoid setting arbitrary dosage limits.

Based on this evidence, the Committee concludes:

Conclusion 2-8: Strong evidence from randomized, double-blind clinical trials, shows that buprenorphine and methadone mainte-

nance treatments have greater efficacy at higher doses. Thus, reasonable clinical guidelines would recommend raising the dose until optimal effects occur, rather than setting arbitrary limits. Studies systematically examining dosing show greater efficacy up to 100 milligrams per day of methadone, and up to 16 milligrams per day of buprenorphine. Doses up to 160 milligrams per day of methadone, and up to 24 milligrams per day of buprenorphine, have been shown to be safe in patients whose dose has been gradually titrated to these levels over a sufficient period of time.

Combined Psychosocial and Agonist Maintenance Treatment for Opiate Dependence

As noted, studies have shown the effectiveness of opioid agonist maintenance therapy in retaining patients in treatment, reducing illicit opiate use, reducing drug-related HIV risk behavior, and protecting against HIV seroconversion. Many developed countries provide MMT in conjunction with some form of psychosocial support, which may also be legally mandated. The Committee reviewed evidence of the effectiveness and added benefit of psychosocial treatments offered with agonist maintenance treatment programs.

Drug use and treatment outcomes: A 2004 Cochrane review (Amato et al., 2004) examined evidence on the effectiveness of psychosocial interventions combined with opioid agonist maintenance treatment, versus opioid agonist maintenance treatment alone. The 12 studies identified for the review covered eight different psychosocial interventions used with agonist maintenance treatment. The authors classified these psychosocial interventions into several categories: behavioral interventions (biofeedback, cognitive behavioral therapy, community reinforcement, and contingency management), psychoanalytic treatments (subliminal stimulation and supportive-expressive therapy), structured counseling, and interpersonal psychotherapy. The review authors concluded that psychosocial interventions added some benefit to opioid agonist maintenance treatment in reducing heroin use, but not in retaining individuals in treatment.

The Committee found the overall evidence in the Cochrane review weak, owing to the poor methodological quality of all but 1 of the 12 studies,[15] and the heterogeneity of the interventions and outcomes. Fur-

[15]The Cochrane review group classified 10 of the 12 studies as having a moderate risk of bias, and 1 as having a high risk of bias (Amato et al., 2004).

thermore, only 1 of the 12 studies addressed the question: Do psychosocial interventions add to the efficacy of opioid agonist maintenance treatment? The remaining 11 studies compared either (1) groups receiving combined psychosocial and agonist maintenance treatment vs. groups receiving psychosocial treatment alone; or (2) groups receiving agonist maintenance treatment with standard drug counseling vs. groups receiving "enhanced" psychosocial services. These study designs did not directly answer the question.

The 1 study (McLellan et al., 1993) of the 12 that was most relevant was an RCT that examined whether the addition of counseling, medical care, and psychosocial services improved the outcomes of opiate-dependent persons enrolled in methadone maintenance treatment. Participants (92 male veterans who were injecting opiate users) were randomly assigned to one of three conditions: (1) minimum methadone services (MMS)—methadone alone (at least 60 milligrams per day) with no other services (n=32); (2) standard methadone services (SMS)—the same dose of methadone plus counseling (n=29); (3) enhanced methadone services (EMS)—the same dose of methadone plus counseling, onsite medical and psychiatric services, employment counseling, and family therapy (n=31).

While MMS was associated with reductions in opiate use, 69 percent of the participants in this group had to be "protectively transferred" to a "treatment-as-usual" condition (which included counseling, thereby approximating the SMS treatment in the trial), because of continued use of opiates or cocaine or the occurrence of several medical or psychiatric emergencies. This result was significantly different from that of the 41 percent of participants in the SMS treatment condition and the 19 percent of participants in EMS who met the criteria for protective transfer. Because patients in SMS were receiving the equivalent of the treatment-as-usual services, and those in EMS were receiving enhanced services, they were not actually transferred.

At the end of the 6-month follow-up period, the 10 individuals who remained in the MMS group showed statistically significant improvement in the drug-use factor score, and the number of days of opiate use, but not on other outcomes. Patients enrolled in the SMS had significantly better outcomes, with significant decreases in both opiate and cocaine use, and some positive but weaker changes in alcohol, legal, family, and psychiatric measures. Finally, EMS patients had the best outcomes, with statistically significant improvement in drug and alcohol use, employment status, illegal activities, family relations, and psychiatric status. Patients assigned to the MMS group who were protectively transferred (n=22) showed significant reductions in cocaine and opiate use after 4 weeks.

When assessing the relative efficacy of the treatments, the investigators excluded individuals in the MMS group who moved to standard treatment

as a result of protective transfer (n=22). In this "as-treated" analysis, 30 percent of the remaining 10 MMS patients were abstinent from opiates and cocaine at 24 weeks, compared with 55 and 68 percent in the SMS and EMS groups, respectively. However, the Committee's "intent-to-treat"[16] reanalysis—which reclassifies individuals in the MMS who were protectively transferred as "treatment failures," and includes them in the overall calculation—shows that the proportion of patients who were abstinent from opiates and cocaine at 24 weeks is actually 9 percent (3/32), versus 55 and 68 percent in the SMS and EMS groups. Based on their analysis, the study authors concluded that counseling improved treatment, and that the addition of other onsite psychosocial services was even more beneficial. The Committee's intent-to-treat reanalysis suggests that the additional benefit of psychosocial services to agonist maintenance treatment is even greater than reported in the original study.

Because virtually all methadone maintenance programs in the United States and other developed countries provide at least some psychosocial intervention (usually drug counseling) in conjunction with agonist treatment, there has been little or no opportunity to further evaluate this issue in these countries. However, developing countries with plans to implement opioid agonist treatment programs can evaluate the effectiveness of adding psychosocial interventions. Furthermore, some developed countries do not require counseling along with buprenorphine maintenance treatment that is provided in office-based settings. Thus investigators in the developed countries may also be able to evaluate these issues. Understanding whether psychosocial interventions in general—and which psychosocial interventions and for which patients in particular—are most effective when combined with agonist maintenance therapy is critical, particularly in countries with constraints on resources and skilled labor.

Based on this evidence, the Committee concludes:

> ***Conclusion 2-9: Most studies have examined the effectiveness of opioid agonist treatment combined with psychosocial treatment, partly because legal mandates in developed countries often require counseling as an integral part of such therapy. As a result,***

[16]The intention-to-treat principle (Hill, 1961) requires that data from all study participants be used in the analysis, regardless of whether they received the assigned treatment or adhered to the protocol (i.e., complied with treatment). The advantage of intent-to-treat analyses is that it provides an unbiased information on the effects of the treatment, rather than biased information resulting from analyses only on a compliant subsample. Although intent to treat analyses are the gold standard in reporting results of RCTs, they are rarely done because of the difficulty in following up on individuals who drop out of treatment early or violate the protocol (Nich and Carroll, 2002).

the additional benefit of adding psychosocial programs to agonist maintenance treatment for opioid-dependent individuals has not been well-studied. Modest evidence from one randomized controlled trial showed that drug counseling plus agonist maintenance treatment is superior to agonist maintenance treatment alone with respect to opiate-dependence outcomes, and that additional onsite psychosocial services further improve outcomes, but more research is needed.

HIV-related outcomes: The Committee identified some studies that examined the effect of psychosocial interventions among patients enrolled in opioid agonist treatment on HIV risk behavior. Four studies included in a meta-analysis (Prendergast et al., 2001), which evaluated the efficacy of combining psychosocial interventions with drug abuse treatment to reduce risk of HIV infection, provided inconclusive results (Courtnage, 1991; Harris et al., 1998; Schilling et al., 1991; Sorensen et al., 1994).

Avants and colleagues (2004) conducted an RCT of the efficacy of a 12-session harm reduction group (HRG) intervention for IDUs that focused on reducing both sex and drug-related HIV risks. Two hundred and twenty patients were randomized to receive either the HRG or a standard care, which included 2 hours of counseling per month and a single risk reduction session. The study found that during treatment, HRG participants were more likely to be abstinent from cocaine and had fewer reports of high-risk sexual behavior. After treatment, HRG patients scored higher on a knowledge test about sex-related risks, and reported higher self-efficacy[17] in high-risk sexual situations. Patients in both groups reported lower injecting drug use and needle sharing.

Baker and colleagues (1993) conducted a randomized trial of a six-session relapse prevention program vs. a brief intervention (one-session motivational interview and self-help booklet) and a control condition among 95 IDUs enrolled in a methadone program. The investigators found that the relapse prevention program was slightly more effective in reducing reported needle sharing during relapse periods. There were no differences between the brief intervention and control groups.

Another study evaluated a voluntary AIDS prevention program for patients attending three methadone maintenance clinics in New York City (Magura et al., 1991). The program included AIDS education seminars,

[17]"Perceived self-efficacy is defined as people's beliefs about their capabilities to produce designated levels of performance that exercise influence over events that affect their lives. Self-efficacy beliefs determine how people feel, think, motivate themselves and behave" (Bandura, 1994).

peer support groups, and HIV counseling and testing. Patients at clinic 1 received all three components, while patients at clinic 2 were not offered HIV testing, and patients at clinic 3 (control) had no special interventions. At the 2-month follow-up, participation in the AIDS education component was associated with greater knowledge of HIV risks and improved reported attitudes toward the use of condoms. Participation in the peer group was associated with improved reported attitudes toward condom use and a reported increase in the use of condoms. Learning that one was HIV-negative was associated with reduced injection-related risks and improved reported self-efficacy. However, the potential for self-selection bias and the low rates of participation (25 percent attended AIDS education, and a lower percentage attended peer groups and was tested) limit the usefulness of the results.

Overall, these studies suggest that psychosocial interventions with patients on methadone help reduce HIV risk behavior, but methodological limitations make the results difficult to interpret.

Based on this evidence, the Committee concludes:

Conclusion 2-10: Few studies have specifically examined the impact of adjunctive psychosocial interventions on HIV risk behavior among patients on opioid agonist maintenance therapy. Weak evidence from several studies suggest that some psychosocial interventions for patients enrolled in such therapy can be effective in reducing sexual and drug-related HIV risk behavior, but more research is needed.

Unintended Consequences of Opioid Agonist Maintenance Therapy

Despite the many benefits of opioid agonist treatments, the medications used for maintenance treatment can be abused. Thus, weighing the risks of expanding access to treatment—notably, the potential for greater misuse and diversion into illicit markets—against the benefits is important. Methadone diversion is associated with a risk of methadone overdose if the methadone is used by individuals who are not tolerant of the dose. Methadone overdose can also occur if methadone doses are too high or increased too rapidly at the start of treatment (Schottenfeld, 2004). Because buprenorphine is a partial agonist, the risk of overdose is considerably lower, but buprenorphine overdose deaths have been reported, particularly when buprenorphine is used along with benzodiazepines (Kintz, 2001; Reynaud et al., 1998).

Although diverted methadone or buprenorphine may be used in a quasi-therapeutic manner to prevent or treat withdrawal symptoms, both medications may also be injected, and thus contribute to the risks of HIV transmis-

sion associated with injecting drug use. Injection of dissolved buprenorphine tablets has been associated with serious adverse effects, including abscesses and optic neuritis (Auriacombe et al., 2004), acute hepatitis among hepatitis C-infected individuals (Berson et al., 2001), and fatalities when combined with benzodiazepines (Kintz, 2001). Arterial ischemia has been reported on rare occasions when buprenorphine is accidentally injected into an artery (Gouny et al., 1999). Injection of methadone can also lead to serious problems and death (Lintzeris et al., 1999; Heinemann et al., 2000; Hopwood et al., 2003).

A number of studies have examined methadone diversion and abuse, particularly in the United States, Europe, and Australia, where methadone has been used for some time. Two recent studies in the United States and in Australia found that large increases in physician prescriptions of methadone tablets for pain management were followed by increased reports of methadone diversion and abuse. The predominant use of methadone tablets in diversion and abuse cases in both areas suggests that methadone tablets were being diverted from the analgesic market rather than from patients attending methadone clinics, with the former providing methadone in syrup or wafer form (Cicero and Inciardi, 2005; Williamson et al., 1997). Germany also experienced an increase in methadone-related overdose deaths, which investigators suggested was due to implementation of a more generous methadone take-home policy for those on maintenance therapy (Heinemann et al., 2000).

Diversion and misuse of buprenorphine have also been observed after its widespread diffusion, particularly in France.[18] France launched an aggressive buprenorphine maintenance therapy program in 1996, in response to a rapid expansion of reported IDU-related HIV cases (Carrieri et al., 2003). The program, which allows general practitioners to prescribe high-dose buprenorphine maintenance treatment, treats an estimated 80,000 addicts (Carrieri et al., 2003).

One study examining illicit drug use and injection practices among patients enrolled in either methadone or buprenorphine maintenance treatment in France found that about 35 percent reported having used an illicit substance, 26 percent reported having injected drugs, and 15 percent reported having injected the agonist drug (buprenorphine or methadone) while in treatment. Risk of injection rose with the dose of buprenorphine, but this was not observed in patients on methadone treatment (Guichard et

[18]In response to concerns about diversion and misuse of buprenorphine, France is considering a controversial proposal to reclassify buprenorphine as a narcotic. The effect that this measure, if implemented, would have on treatment access and availability is unclear. [Online]. Available: http://opiateaddictionrx.info/whatsnew.asp?id=1186 [accessed July 31, 2006].

al., 2003). Despite the relatively high prevalence of injection buprenorphine abuse among these patients, it is not clear whether buprenorphine maintenance increased the risks in these patients. It is possible that maintenance treatment may have reduced overall injection drug use in the population treated as well as the frequency or dangers associated with injection drug use even in those who continued injection drug use while being maintained on buprenorphine.

In a cross-sectional study of a sample of IDUs recruited from pharmacies, needle-exchange programs, and vending machine sites in France, 34 percent of respondents reported occasionally injecting buprenorphine, and 24 percent reported injecting only buprenorphine in the past 6 months (Obadia et al., 2001). In a cohort study of 114 HIV-infected IDUs, 28 percent reported buprenorphine injection misuse during the study period. Analysis showed that buprenorphine injectors were more likely to be multiple drug users and depressed, and less likely to be receiving antiretroviral treatment (Carrieri et al., 2003). In another study, nearly 50 percent of drug addicts interviewed in a cross-sectional survey reported injecting buprenorphine (Varescon et al., 2002).

One major strategy for reducing misuse and diversion of buprenorphine has been the development of a tablet combining buprenorphine and the opioid antagonist naloxone (Suboxone). The combination drug is currently being used in several countries. When the combination tablet is taken sublingually as prescribed, all the buprenorphine but very little naloxone is absorbed, so the naloxone does not have any clinical effects or interfere with the effects of buprenorphine (Kosten et al., 1990; Mendelson et al., 1999). However, when the buprenorphine/naloxone combination is dissolved and then injected, the naloxone takes full effect and will precipitate withdrawal symptoms for people who are dependent on heroin or other opioids (Mendelson et al., 1999; Elkader and Sproule, 2005). By causing withdrawal in heroin-dependent individuals, the combination drug offers better protection against misuse than the mono-buprenorphine tablet, but it is not a foolproof solution (Comer and Collins, 2002). When injected, the naloxone reduces the pleasurable or reinforcing effects of the buprenorphine only partially (Comer and Collins, 2002). And because buprenorphine binds more tightly to opiate receptors than naloxone, injected naloxone may not precipitate withdrawal in buprenorphine-dependent individuals (Kosten et al., 1990; Mendelson et al., 1999). As a result, the combination product may be abused, especially by individuals who are not physically dependent on heroin or other opioids, or by individuals who are physically dependent on buprenorphine.

There are clear societal-level tradeoffs between making opioid agonists more available, less costly to administer, and less burdensome on patients (such as through take-away doses and physician prescriptions) and reduc-

ing diversion and misuse. Specifically, increasing the number or proportion of opioid dependent individuals who are treated with opioid agonist maintenance treatment and increasing the retention of these patients in treatment increases the public benefits of opioid agonist maintenance treatment with regard to reductions of illicit opioid use, drug-related HIV risk behaviors, and HIV transmission.

A recent study in Australia (Ritter and Di Natale, 2005) examined this tradeoff by comparing methadone take-away policies and rates of methadone injection across six states. The study found that states with more restrictive take-away policies had lower reported rates of methadone injection. However, the investigators also found that methadone injection rates varied substantially among states with similar take-away policies. Factors that appear to be important include not only take-away policies but also drug preference, drug availability, treatment availability, and the amount of treatment coverage. This study illustrates the importance of taking into account both the benefits and the risks when making policy decisions on access to opioid agonist treatments.

Based on this evidence, the Committee concludes:

Conclusion 2-11: Strategies to limit diversion of opioid agonist medications—such as limiting the number of physicians who can prescribe the medication or directly observing patients while they ingest the medication—may increase the costs of treatment, and the costs to and burdens on patients, and may thus limit the dissemination of opioid agonist maintenance treatment. Countries' policies and regulations regarding opioid agonist maintenance treatment should balance the potentially competing goals of increasing the accessibility and utilization of opioid agonist maintenance treatment and reducing the likelihood of diversion of agonist maintenance medications.

OPIOID ANTAGONIST PHARMACOTHERAPY

Opioid antagonist medication is another treatment option for opioid-dependent individuals who will not accept or cannot access opioid agonist maintenance therapy. Naltrexone is the most commonly used and widely studied opioid antagonist medication used to help the individual maintain long-term abstinence from opioids following detoxification.[19] Studies show high relapse rates among opioid-dependent patients who simply undergo

[19]The shorter-acting opioid antagonist medication, naloxone, is widely used to treat overdose.

detoxification and are not provided additional pharmacological or psychosocial treatments (IOM, 1990). Moreover, by lowering tolerance, detoxification appears to raise risks of overdose mortality among those who resume opioid use (Strang et al., 2003). As discussed later in this chapter, psychosocial interventions have little efficacy for opioid-dependent patients who are not receiving pharmacotherapy.

Oral naltrexone provides relatively long-lasting (up 1–3 days depending on dose) blockade of euphoric or rewarding effects of heroin or other opioids, and thus may help prevent resumption of opiate use (O'Brien and Kampman, 2004). New long-acting, injectable formulations of naltrexone produce adequate opioid blockade for up to 1 month (Dunbar et al., 2006). Before beginning naltrexone treatment, patients must be detoxified (medically withdrawn from heroin or other opioids), because naltrexone will precipitate severe withdrawal symptoms in people physically dependent on opioids (O'Brien and Kampman, 2004). Naltrexone binds tightly to opiate receptors, but does not activate them or have any rewarding, mood-altering, or euphoric effects, or lead to withdrawal symptoms when it is discontinued (O'Brien and Kampman, 2004). Because naltrexone's blockade of opiate effects can be overridden by sufficiently large doses of opioids, naltrexone decreases but does not eliminate the risk of opioid overdose (O'Brien and Kampman, 2004). Patients who discontinue naltrexone are at greater risk for overdose if they resume opioid use (O'Brien and Kampman, 2004; Digiusto et al., 2004).

Despite strong pharmacological evidence and theoretical potential for naltrexone, evidence regarding its efficacy in controlled clinical trials is inconclusive. High attrition (premature discontinuation of treatment) is common with naltrexone treatment, and that complicates evaluation of its efficacy (Minozzi et al., 2006). The effectiveness of naltrexone in clinical practice, and consequently also the impact of naltrexone treatment for reducing drug use and HIV transmission on a large scale in the population of opioid-dependent individuals, has also been limited by high attrition, the relatively limited patient appeal of naltrexone, and the need for medically supervised withdrawal and a period of sustained abstinence before treatment begins (Kirchmayer et al., 2003).

In a recent Cochrane review (Minozzi et al., 2006), investigators conducted a meta-analysis of 10 RCTs comparing the efficacy of naltrexone treatment vs. placebo and other psychosocial treatments in preventing relapse in opioid-dependent persons after detoxification. Some of the studies compared naltrexone plus behavioral therapy with placebo plus behavioral therapy, or with behavioral therapy alone.

Four of the studies were conducted in the United States, two in Israel, and one each in Spain, China, Russia, and Germany. Two studies had adequate allocation concealment (Krupitsky et al., 2004; Lerner et al.,

1992). Seven of the ten trials were double-blind controlled trials (Curran and Savage, 1976; Guo et al., 2001; Hollister, 1978; Krupitsky et al., 2004; Lerner et al., 1992; San et al., 1991; Shufman et al., 1994), and three were not (Cornish et al., 1997; Ladewig, 1990; Rawson et al., 1979). Naltrexone dosage and frequency of administration varied by study.

All trials were conducted on an outpatient basis. The mean duration of trial length was 6 months, with a range of 1 to 10 months. The meta-analysis did not include data from one of the larger studies (Hollister et al., 1978) because the authors did not specify the number of participants in each treatment group.

Primary outcomes examined in the Cochrane meta-analysis included successful retention in treatment, opioid use during treatment, and relapse rates at follow-up. Secondary outcomes included side effects and reincarcerations during the study period. The analysis found that naltrexone treatment combined with psychosocial therapy was more efficacious than placebo alone, or placebo plus psychosocial, in reducing heroin use during treatment (RR 0.72; 95% CI: 0.58–0.90). However, the statistical significance of the results disappeared in comparisons of naltrexone therapy alone vs. placebo (RR 0.79; 95% CI: 0.59–1.06). Naltrexone plus psychosocial therapy was more effective than psychosocial treatment alone in preventing reincarceration during the study period (RR 0.50; 95% CI: 0.27–0.91). Naltrexone did not have a statistically significant benefit on retention in treatment, side effects, or relapse results at follow-up for any of the comparisons.

Johansson and colleagues (2006) conducted a recent meta-analysis of 15 RCTs comparing naltrexone with control populations. The authors found significant heterogeneity in the efficacy of naltrexone across trials. Treatment retention was the key explanatory variable for this heterogeneity. While naltrexone-treated groups had significantly fewer opioid-positive urine tests than controlled counterparts, this effect was only seen in the patient subgroup with high treatment retention. Contingency management[20] (see next section on psychosocial interventions) was found to increase both retention and naltrexone use.

One RCT published since these reviews examined the efficacy of naltrexone with and without fluoxetine in preventing relapse among 280 heroin addicts in St. Petersburg, Russia. All patients received drug counseling and had involvement from parents or significant others. At 6 months,

[20]Contingency management entails consistently rewarding patients (e.g., with monetary vouchers or other salient positive reinforcers) who remain abstinent or successfully complete other verifiable treatment objectives, and withholding rewards when a patient does not abstain (or successfully accomplish other specified objectives).

the number of people in the naltrexone treatment group who remained in treatment and were relapse-free was two to three times greater than the number of patients in the naltrexone placebo group (OR=3.5; 95% CI: 1.96–6.12). Adding fluoxetine did not improve outcomes. Retention was still a problem in this study, but reportedly less than in prior U.S. studies. The study found a decrease in HIV risk behaviors, psychiatric symptoms, and overall adjustment among patients who remained in treatment and did not relapse, although the possibility of self-selection bias cannot be excluded because follow-up was possible on only 40 percent of those who dropped out of treatment.

Several studies evaluating naltrexone in special populations—including patients on supervised probation (Cornish et al., 1997), or opioid-addicted physicians or lawyers (Tennant et al., 1984; Washton et al., 1984) whose ability to continue to work is contingent on abstinence—provide evidence that naltrexone may be efficacious under certain circumstances. Naltrexone has also been suggested as a potential intervention option in Russia, because opioid agonist maintenance treatment is illegal, and because many heroin addicts are young people who live with their parents who can oversee their medication adherence (Krupitsky et al., 2004, 2006). These studies suggest that naltrexone may be efficacious when used in circumstances where patients' medication adherence and treatment retention can be closely monitored and facilitated.

Some studies also suggest that the efficacy of naltrexone can improve when it is combined with behavioral family therapy (O'Farrell and Fals-Stewart, 2002; Krupitsky et al., 2006) or contingency management (Carroll et al., 2002). New long-acting, injectable formulations may also improve the efficacy and effectiveness of naltrexone in clinical practice, as patients would be protected for several weeks after the last injection, providing enough time for clinics to reengage patients in treatment and provide the next dose before they relapse (Dunbar et al., 2006). However, the efficacy of these formulations has not yet been systematically evaluated.

Based on this evidence, the Committee concludes:

Conclusion 2-12: While there is strong pharmacologic evidence that naltrexone blocks opiate effects, its efficacy in controlled clinical trials is inconclusive. Efficacy and effectiveness studies of naltrexone treatment have been limited by problems with high patient attrition and the limited appeal of naltrexone. Studies suggest that naltrexone may be efficacious when used in circumstances where patients' medication adherence and treatment retention can be closely monitored and facilitated.

PHARMACOTHERAPIES FOR STIMULANT DEPENDENCE

No pharmacological treatments have been found to be consistently efficacious in treating stimulant dependence. The National Institute on Drug Abuse in the United States is conducting a major research effort to identify effective pharmacotherapies for cocaine dependence (Vocci and Elkashef, 2005). Several studies suggest that disulfiram, an aversive drug therapy used to help prevent relapse among alcoholics, has potential as a treatment for cocaine use (Suh et al., 2006; Vocci and Elkashef, 2005). A number of randomized controlled trials of disulfiram support its efficacy in reducing cocaine and alcohol use and improving treatment retention among non-alcoholic cocaine-dependent and cocaine-alcohol dependent people (Higgins et al., 1993; Carroll et al., 1998, 2000). A recent study found that the benefits of disulfiram were strongest for cocaine users who did not have concurrent alcohol dependence, or who fully abstained from drinking during treatment (Carroll et al., 2004). Disulfiram has also been shown to reduce cocaine use among cocaine-dependent people enrolled in opioid agonist therapy, suggesting the possibility of combining pharmacotherapies (Petrakis et al., 2000; George et al., 2000). However, potential liver toxicity, nerve toxicity, and serious safety concerns about disulfiram-alcohol interactions, especially if cocaine is also used, may limit its use (Chick, 1999; Enghusen et al., 1992; Suh et al., 2006). Disulfiram is not approved by the U.S. Food and Drug Administration or other regulatory agencies for treatment of cocaine dependence.

Several other medications, including baclofen, modafinil, tiagabine, and topiramate, have also shown initial efficacy in reducing cocaine use in controlled clinical trials of cocaine-dependent patients. However, confirmatory trials are needed to replicate these results (Vocci and Elkashef, 2005). Current evidence does not support the clinical use of dopamine agonists, carbamazepine, and antidepressants for treating cocaine dependence (Soares et al., 2003; Lima Reisser et al., 2002; Lima et al., 2003).

Compared with the extensive research on pharmacotherapies for treating heroin and cocaine dependence, research on pharmacotherapies for dependence on amphetamine-type stimulants (e.g., methamphetamine) has only recently increased (Colfax and Shoptow, 2005). While several observational studies have examined the effects of stimulants prescribed to treat methamphetamine use, the only RCT testing the efficacy of a stimulant agent, dextroamphetamine, found no significant difference between the treatment and placebo arms, although both reduced their methamphetamine use (Colfax and Shoptow, 2005). A Phase II trial to treat methamphetamine dependence with buproprion, an antidepressant, is under way (Colfax and Shoptow, 2005). Phase I trials of vigabatrin, an anticonvulsant, showed decrease use of methamphetamine among those completing the trial, but attrition was high (Colfax and Shoptow, 2005). Randomized

controlled trials of other pharmacological agents[21] found no effects on the use of methamphetamine or amphetamine-type stimulants (Srisurapanont et al., 2001; Rawson et al., 2002; Colfax and Shoptaw, 2005). Because of the widespread problem of methamphetamine abuse in many areas of the world, particularly Southeast Asia, additional research on pharmacotherapies for stimulant abuse is needed.

Based on this evidence, the Committee concludes:

Conclusion 2-13: No pharmacotherapy has been found to be consistently efficacious in treating stimulant dependence. There is modest to moderate evidence for the efficacy of disulfiram in reducing cocaine use, but liver toxicity, nerve toxicity and serious safety concerns related to potential disulfiram-alcohol-cocaine interactions may limit its value as a potential treatment. There is weak evidence regarding the efficacy of other pharmacological treatments for treating cocaine dependence. Research on pharmacotherapies for amphetamine-type stimulants has been limited and no effective therapies have been identified. More research is needed to further develop and define effective approaches to treat stimulant dependence.

EFFICACY AND EFFECTIVENESS OF PSYCHOSOCIAL INTERVENTIONS

A second major approach to drug treatment involves psychosocial interventions, which include a broad range of psychological and behavioral strategies, used either alone or in combination with pharmacotherapies and other medical or social interventions (Mayet et al., 2004). Psychosocial interventions may be provided with varying levels of intensity and frequency, for varying durations, and using a variety of approaches in outpatient treatment programs, partial hospital programs, in-hospital or residential programs. Psychosocial interventions may be delivered in individual or group settings, and may also include family members in the treatment in order to address family functioning (e.g., behavioral family therapy). Because proven pharmacological interventions are only available for treatment of opioid dependence[22] and not for stimulants or other injectable drug

[21]Agents that have been tested include: fluoxetine, a serotonin reuptake inhibitor; imipramine and desipramine, tricyclic antidepressants; amlodipine, a calcium channel blocker; and ondansetron, a seotonergic antagonist (Srisurapanont et al., 2001; Colfax and Shoptaw, 2005).

[22]The focus of this report is on injecting drug users, and opiates are the only injectable drugs for which pharmacological treatments are available.

classes, psychosocial approaches are the primary treatment option for individuals dependent on these substances.

In this section, the Committee reviews the evidence regarding the effectiveness of the major psychosocial approaches to drug dependence treatment. These include four specific behavioral interventions (contingency management, community reinforcement approach, cognitive behavioral therapy, and motivational interviewing) as well as a collection of program models that include therapeutic communities, narcotics or drug anonymous programs (12-step programs), and chemical dependency programs (see Box 2.2 for a description of interventions). Evaluations of psychosocial programs are complicated by the significant heterogeneity of interventions and patient populations across sites.

Behavioral Interventions

Contingency Management

Contingency management (CM) has been extensively studied and shown to be effective in the treatment of stimulant-dependent individuals. CM relies on a variety of rewards, including monetary vouchers that can be redeemed for goods and services if the patient's urine tests are free of illicit drugs, social rewards, or for methadone-maintained patients with co-occurring stimulant dependence, take-home methadone doses contingent on abstinence. When monetary vouchers are provided, the voucher amount typically rises with the number of consecutive drug-free urine tests, but starts over at a low amount if a person has a drug-positive test. The cumulative sum of the vouchers can reach several thousand dollars for long periods of abstinence. A lower-cost alternative—in which patients can draw from a prize lottery—has also been evaluated and is discussed below (Peirce et al., 2006; Petry and Martin, 2002).

A number of studies have shown the efficacy of CM for drug use and other outcomes among individuals with primary dependence on stimulants (Higgins et al., 1991, 1993, 1994, 2000; Petry et al., 2004), and among individuals who are dependent on both opiates and stimulants and receiving methadone (Piotrowski et al., 1999; Schottenfeld et al., 2005; Peirce et al., 2006). A lower-cost, prize-based CM procedure has also been found efficacious in treating primary cocaine dependence (Peirce et al., 2006) and cocaine dependence in opioid-dependent patients treated with methadone maintenance (Petry and Martin, 2002).

While researchers have studied the efficacy of CM among cocaine users extensively, the approach has not been as well-studied among users of other stimulants, such as methamphetamine. One study conducted in the United States found that CM interventions were efficacious in reducing metham-

BOX 2-2 Psychosocial Interventions for Drug Dependence Treatment

Specific Behavioral Interventions

Contingency management (CM) entails consistently rewarding patients (e.g., with monetary vouchers or other salient positive reinforcers) who remain abstinent or successfully complete other verifiable treatment objectives, and withholding rewards when a patient does not abstain (or successfully accomplish other specified objectives) (Higgins et al., 1991, 1993, 1994, 2000).

Cognitive behavioral therapy (CBT) teaches patients to recognize the environmental, interpersonal, stress-related, and psychological triggers—or cues—that lead to craving or relapse and to make lifestyle changes that support abstinence. Patients are also taught to identify the behavioral chains that lead to relapse and the coping skills to manage craving without relapse, and to avoid high-risk situations (Carroll et al., 1994).

Community reinforcement approach (CRA) is based on the theory that certain drug-related reinforcers (e.g., the positive drug effects or the social relationships organized around drug use) and a lack of non-drug-related alternatives maintains dependence. Thus, behavioral counseling is used to help patients develop or enhance rewarding activities, work, friendships, and other social interactions unrelated to drug use. The counseling also incorporates all the components of cognitive behavioral therapy. Patients are also provided vocational counseling and job-seeking skills, and helped to obtain employment or engage in other productive, nondrug-related activities (Higgins et al., 1991, 1993, 1994, 2000).

Motivational interviewing (MI) is a brief intervention that helps patients identify and resolve areas of ambivalence about continuing or ceasing drug use, thereby enhancing their desire or motivation to change. This strategy is based on the

phetamine use. In this randomized controlled trial (Shoptaw et al., 2005), 162 methamphetamine-dependent gay and bisexual men in Los Angeles were randomly assigned to one of four treatment conditions for 16 weeks. These conditions included standard cognitive behavioral therapy (CBT, n=40), contingency management (n=42), combined CBT and CM (n=40), and culturally adapted CBT (n=40). The study showed that interventions that included CM were most effective in retaining patients in treatment and reducing methamphetamine use. The CM condition produced the most methamphetamine-free urine samples, compared with standard CBT, followed by CBT plus CM, and then culturally adapted CBT.

Another recent RCT study evaluated the efficacy of sertraline[23] and

[23]Sertraline (Zoloft®) is a selective serotonin reuptake inhibitor commonly used to treat depression.

theory that there are five stages that people progress or cycle through in the process of achieving steady change: precontemplation (prior to recognition of problems associated with drug use or prior to beginning to think about stopping), contemplation (considering the benefits and losses of continuing drug use or stopping drug use), preparation for change, action (taking steps to stop drug use and then stopping use), and maintenance (preventing relapse) (Miller and Rollnick, 1992).

Matrix model is a manual-based treatment protocol that includes 16 weeks of CBT, family education groups, social support groups, and individual counseling, combined with weekly testing for alcohol and other drugs (Rawson et al., 2004).

Program Models

Therapeutic community model began in California in the 1950s and uses a structured residential community, organized around a peer hierarchy (with successful residents taking on increasing leadership roles) to confront patients about maladaptive behaviors and encourage and teach patients to cope with disappointments, loss, anger and other stressors without resorting to drug use or other maladaptive behaviors (IOM, 1990).

Chemical dependency model derives from a hospital-based approach to treating alcoholism that emphasizes 12-step recovery, developed in Minnesota in the 1960s, and therefore often referred to as the Minnesota model (IOM, 1990).

12-step recovery approaches (e.g., Narcotics Anonymous) use peer-led recovery groups to encourage addicts to acknowledge their addiction, recognize addiction as a disorder with medical, psychological, and spiritual components; these groups support addicts to take steady steps toward recovery by following the guiding principles initially established for Alcoholics Anonymous (IOM, 1990).

contingency management for the treatment of methamphetamine dependence among a group of male and females from the west coast of the United States (Shoptaw et al., 2006). Participants (n=229) were randomized to one of four conditions for 12 weeks: (1) sertraline (50 milligrams twice a day) plus CM (n=61); (2) sertraline only (n=59); (3) placebo plus CM (n=54); or (4) placebo only (n=55). The findings did not support the use of sertraline, however, they did support the use of CM for treating methamphetamine dependence. The study found that a significantly higher proportion of participants in the CM conditions achieved three weeks of methamphetamine abstinence than those in the non-CM conditions.

Although there is strong evidence regarding the efficacy of CM for treating cocaine dependence and moderate evidence from two RCTs of its efficacy for treating methamphetamine dependence, it has not been found to be efficacious for individuals who are addicted to opiates alone and who

are not enrolled in agonist maintenance treatment. One study (Katz et al., 2002) that examined the use of CM for treating opiate-dependent individuals not on methadone had negative findings. This study compared two groups of opiate-dependent individuals referred from local detoxification units who were randomly assigned to either a voucher (n=29) or a no-voucher (n=23) condition. Both groups also received intensive cognitive behavioral therapy. Participants assigned to voucher could receive more than $1,000 for submitting urine samples that were both opiate and cocaine free.

The study found no differences between the voucher and no-voucher groups in treatment retention, number of opiate and cocaine-negative urines, or longest periods of abstinence. Retention in both groups averaged less than 40 days, of 180 days of treatment planned. The average maximum period of consecutive abstinence in both groups was less than 17 days, and only 21 percent of patients assigned to vouchers (and 9 percent of those assigned to the no-voucher control) remained abstinent for four or more weeks. Given the efficacy of CM in treating stimulant dependence (see below), and when combined with opioid agonist maintenance for treating co-occurring cocaine and opioid dependence, these negative findings point to the difficulty of treating opioid-dependent patients without opioid agonist maintenance treatment.

Cognitive Behavioral Therapy

In CBT, patients are taught to recognize the antecedents of drug use (e.g., environmental, interpersonal, stress-related, and psychological triggers—or cues—that lead to craving or relapse) and consequences of drug use and to learn skills and make behavioral changes to achieve and sustain abstinence. Patients are taught to identify the behavioral chains that lead to relapse, encouraged to make lifestyle changes that promote abstinence and avoid high-risk situations, and taught the coping skills to manage craving without relapse. Cognitive behavioral therapy has been evaluated for the treatment of a variety of addictive disorders, including alcohol, cocaine, nicotine, and marijuana dependence. Findings from several RCTs provide support for the efficacy of CBT for treating cocaine dependence, although differences in the outcome measures utilized, comparison treatments, and study methodologies complicate systematic comparison (Maude-Griffin et al., 1998; Monti et al., 1997; McKay et al., 1997; Carroll et al., 1994). A recent RCT found CBT to be more efficacious than interpersonal psychotherapy in reducing cocaine use (Carroll et al., 2004). Results of several RCTs indicate that CBT effects persist after cessation of counseling (Rawson et al., 2002; O'Malley et al., 1996; Carroll et al., 1994 2000).

Community Reinforcement Approach

Most studies of the community reinforcement approach have been conducted with cocaine-dependent individuals and have bundled CRA counseling with contingency management and disulfiram treatment for individuals with co-occurring alcohol problems (Higgins et al., 1991, 1993, 1994, 2000). One RCT found that CRA (including CM) was more efficacious than CM alone in retaining individuals in treatment and keeping them abstinent from cocaine (Higgins et al., 2003; Roozen et al., 2004), supporting the efficacy of the CRA counseling components over and above CM.

Motivational Interviewing

Motivational interviewing uses an empathic, non-confrontational approach to increase patients' recognition of the harmful effects or consequences of their drug use and their motivation and resolve to reduce or abstain from drugs (Miller and Rollnick, 1992). Motivational interviewing or motivational enhancement treatment has been investigated as a brief, stand-alone treatment for problem drinking and alcohol dependence. Several RCTs support its efficacy for reducing heavy drinking in problem drinkers who are not alcohol dependent and indicate that its efficacy for treating alcohol dependence is comparable to CBT or 12-step facilitation, a counseling approach designed to encourage patients to become involved in and utilize effectively 12-step recovery groups (Sellman et al., 2001; Project MATCH Research Group, 1998; Burke et al., 2003). Motivational interviewing has not been as thoroughly investigated for treating stimulant or opioid dependence, and promising findings from preliminary studies (Stotts et al., 2001; Secades-Villa et al., 2004) have not yet been validated with larger RCTs (Rohsenow et al., 2004).

Individual Counseling Promoting Utilization of 12-Step Recovery Programs and Involvement in the Tasks and Goals of 12-Step Recovery Programs

Twelve-step facilitation and the individual drug counseling utilized in the National Institute on Drug Abuse (NIDA) multi-site, randomized clinical trial of psychosocial treatments for cocaine dependence promote involvement in 12-step recovery programs and utilization of the strategies, goals, and principles of these recovery groups. In the NIDA multi-site cocaine collaborative treatment study, adding individual counseling to group drug counseling improves outcomes (addiction severity index composite score and length of time abstinent) for cocaine users compared to patients receiving group counseling only or group counseling combined with indi-

vidual cognitive therapy or individual interpersonal therapy (Crits-Christoph et al., 1999).

Matrix Model

The matrix model is an intensive program that combines several of the above treatments. It is a manual-based treatment protocol that includes 16 weeks of CBT, family education groups, social support groups, and individual counseling, combined with weekly testing for alcohol and other drugs.

In the largest clinical trial (Rawson et al., 2004) of treatment for methamphetamine dependence, 978 participants were randomly assigned to either treatment as usual or a 16-week treatment based on the matrix model at eight community outpatient settings in the western United States. Because the intention was to compare the matrix model with real-world treatment, the treatment-as-usual programs were not standardized. Instead, they encompassed a range of programs with varying approaches and intensity, including a "best available option" and a "minimal contact program."

Overall, participants assigned to the matrix model attended more treatment sessions (except at a drug-court site) and remained in treatment significantly longer (five of the eight sites). Participants assigned to the matrix model provided more methamphetamine-free urine samples during treatment (except at the drug-court site) and had longer periods of methamphetamine abstinence. However, the differences in the number of methamphetamine-free urine samples were significant at only one site, and the differences in duration of abstinence were significant at only two sites. Participants at all sites showed significant improvement in drug use and functioning scores at discharge and 6 months post-admission follow-up, compared with baseline levels. The matrix approach was not superior on these measures.

Based on this evidence, the Committee concludes:

> ***Conclusion 2-14: 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 primarily 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 but who are not enrolled in agonist maintenance therapy. While most studies have examined the efficacy of CM for cocaine users, two randomized clinical trials show that CM is effective in reducing methamphetamine use.***

Conclusion 2-15: There is modest evidence of efficacy of several other behavioral approaches to addressing stimulant abuse. These include combined individual drug counseling and intensive group drug counseling, cognitive behavioral therapy, and community reinforcement combined with contingency management. There is weak evidence regarding the effectiveness of motivational interviewing and the matrix model for treatment of stimulant or other drug dependence. No psychosocial intervention alone (in the absence of pharmacotherapies) has been shown to be consistently efficacious in treating opioid dependence.

Therapeutic Communities, Narcotics or Drug Anonymous Programs, and Chemical Dependency Programs

The Committee also reviewed evidence regarding the effectiveness of Narcotics Anonymous (NA) and other self-help or 12-step recovery programs; therapeutic communities (TC), which involve longer-term residential treatment; and chemical dependency programs, which are 12-day or 28-day inpatient and residential approaches (IOM, 1990). The Committee recognizes that many individuals who have achieved lasting recovery from addiction to heroin or other opioids and other drugs have used NA, chemical dependency programs, or TC to initiate and support their recovery. Nevertheless, the efficacy and effectiveness NA—alone or in combination with other approaches—has not been systematically evaluated.

A 1990 IOM report, *Treating Drug Problems,* reached the following conclusion about NA: "There are virtually no data to answer critical questions regarding independent self-help fellowship groups such as Narcotics Anonymous and Cocaine Anonymous" (p. 135). This report also noted that NA and other Drug Anonymous groups are often "in essence part of the environmental baseline over which the incremental effects of the more formal treatments must be measured" (p. 135).

High relapse rates following detoxification—even when patients are given drug counseling and referred to NA—suggest that for the vast majority of addicts, any given episode of detoxification, drug-free counseling, or NA is not likely to lead to sustained abstinence or recovery. Over time, repeated relapse and treatment episodes may lead to sustained recovery for a growing number of individuals, but data from long-term, naturalistic follow-up studies of treated addicts document the risks of addiction and the difficulties of achieving sustained recovery.

Hser and colleagues (2001) reported the status of 581 heroin-addicted men more than 30 years after their admission to compulsory drug abuse treatment. Nearly half of the men had died within this period—most as a result of drug overdose, suicide, violence, accidents, infections, or chronic

liver disease. The mortality rate greatly exceeded that expected for men in their 20s and 30s at the time of the cohort assembly. After more than 30 years, only 23 percent of the men were not using illicit opiates. Reflecting the persistence of addiction and the high risk of relapse, only about one of six of those who were continuing to use 20 years after admission—and about the same proportion of those who had been abstinent for less than 5 years at that time—were abstinent after another 10 years. One-quarter of those who had been abstinent for more than 15 years at the 20-year follow-up also relapsed over the next 10 years.

It is important to distinguish TC from long-term detention or imprisonment. There are limited or no data from controlled clinical trials regarding the efficacy of long-term detention for preventing post-detention relapse. Naturalistic studies from many countries report exceedingly high relapse rates following prison release. For instance, relapse rates among inmates in government-run drug rehabilitation centers in Malaysia reportedly range from 70 to 90 percent (Reid et al., 2005; Scorzelli, 1992). In contrast, however, follow-up studies of patients treated in a TC consistently report that longer time in treatment is associated with higher proportion of patients abstinent at follow-up (IOM, 1990). This may be due to self-selection: that is, patients with poor prognosis may drop out of treatment early, while patients with good prognosis may stay in treatment.

The major limitation in evaluating the effects of TC relative to other treatments is the high attrition rate. As noted in the 1990 IOM report, "Conclusions about the effectiveness of TCs are limited by the difficulties of applying standard clinical trial methodologies to a complex, dynamic treatment milieu and a population resistant to following instructions. Randomized trials or natural experiments in the community, which would permit a well-controlled comparison of clients admitted to TC treatment versus an equivalent group . . . are not feasible or appropriate; when attempted, such experimental protocols have failed" (see Bale et al., 1980, p. 153).

Consequently, data on the effectiveness of TCs are derived mainly from prospective cohort studies of patients entering TCs or other types of drug treatment. Most such studies show a strong association between length of time in treatment and better outcomes at long-term follow-up (IOM, 1990). Patients staying in TCs longer than 90 days have better treatment outcomes (in terms of drug use, employment, and criminal activity), and the longer patients remain in treatment beyond 90 days, the better the outcomes. Data from the U.S.-based Treatment Outcome Prospective Study indicated that staying 1 year or more in a TC was significantly associated with better drug, employment, and criminal activity outcome measures at 1-year post-treatment follow-up. Data from the Drug Abuse Treatment Outcome Studies, a longitudinal study of 96 treatment programs in the United States, also

supported a relationship between treatment duration and improved outcomes. Data collected at 5-year follow-up showed that staying more than 6 months in long-term residential treatment was associated with significant reductions in drug use and illegal activities, and significant increases in full-time employment (Hubbard et al., 2003).

Thus findings from these prospective cohort studies regarding the effectiveness of chemical dependency outpatient treatments are similar to the findings for TCs: "Clients who remain in treatment longer have better outcomes at follow-up than shorter term clients" (IOM, 1990, p. 168).

Based on this evidence, the Committee concludes:

Conclusion 2-16: There is relatively weak evidence regarding the effectiveness of therapeutic communities, chemical dependency programs, and drug anonymous treatments, but these are important treatment options for opioid-dependent individuals who will not accept or cannot access opioid agonist maintenance treatment, or for individuals dependent on other classes of drugs.

Conclusion 2-17: Studies have found that length of time in treatment in therapeutic communities, chemical dependency, or outpatient programs is the strongest predictor of positive treatment outcomes. However, the possibility of self-selection bias cannot be excluded.

Effects of Psychosocial Interventions on HIV-Related Outcomes

Stimulant-addicted individuals are at high risk for HIV transmission, primarily because of sexual risk behavior, including high-risk sex associated with stimulant use, and—for those who inject stimulants—injecting drug use. The Committee identified two reviews and meta-analyses that specifically examined the impact of psychosocial interventions on the HIV-related risks of injecting drug users. Both these studies suggest that psychosocial interventions have some positive effect on behavioral change (Prendergast et al., 2001; Gibson et al., 1998). However, it is difficult to interpret the findings of these reviews because the studies included different types of psychosocial interventions, drug users (stimulant and opiate users), and patient populations (residential, outpatient, methadone-maintained).

The recent meta-analysis by Prendergast and colleagues (2001) on the efficacy of adding psychosocial interventions targeting HIV risk reduction to drug counseling identified 18 studies comparing an intervention group and a comparison group. The results of the meta-analysis suggest that these added interventions may reduce overall HIV risk behavior and sexual risk behavior, and may increase HIV risk-reduction skills. However, the conclu-

sions of the review are weakened because of the heterogeneity of the interventions and the patient populations. Some studies included methadone-maintained patients, others included patients in hospital or residential programs, and still others included patients in outpatient programs.

Gibson et al. (1998) similarly reviewed 19 studies examining the effectiveness of individual counseling, HIV testing, group interventions, street outreach, and social intervention designed to change behavioral norms. The results of this analysis also pointed to a beneficial effect of psychosocial interventions on behavioral change. Again, however, the results of the analysis are limited because of the heterogeneous interventions and patient populations.

As noted, one study by Shoptaw and colleagues (2005) examined the effect of CM, standard CBT, and an intervention that integrates CBT with culturally tailored counseling targeting sexual risk behavior among methamphetamine-addicted men who have sex with men (gay-specific CBT, or GCBT) in the United States. Participants in the culturally adapted GCBT had statistically significant reductions in unprotected receptive anal intercourse in the first 4 weeks of treatment. Participants in all treatment conditions reported significantly reduced levels of unprotected anal intercourse and the number of sex partners from baseline to 16 weeks. Decreases in reported sexual risk behavior were maintained at 6-month and 12-month follow-ups. The study detected no statistically significant differences between groups.

Based on this evidence, the Committee concludes:

Conclusion 2-18: Weak to modest evidence shows that targeted psychosocial interventions are effective in reducing sex-related HIV risk behavior among stimulant-dependent individuals.

LINKS TO HEALTH AND SOCIAL SERVICES

Drug treatment services are often provided in specialized drug treatment clinics, that are typically separate from other health and social services (WHO et al., 2004). Opioid agonist treatments, particularly methadone, are highly regulated in many countries and administration may be limited primarily to licensed narcotic treatment programs. Some countries, particularly in Western Europe, have made physician office-based treatment of opioid agonist treatments widely available. Other drug treatment programs (e.g., chemical dependency, therapeutic communities) provided in outpatient, inpatient, or residential settings may incorporate or provide referrals to additional medical or social services, but the availability of these services varies substantially across sites (IOM, 1990).

Few studies have specifically examined whether participation in drug-

dependence treatment leads to increases in the use of needed health and social services. Several studies from the United States have examined whether delivery of outpatient primary care at the site of drug-dependence treatment reduces expensive visits to the emergency department and inpatient hospitalization, both of which are indicators of poor access to care and/or poor quality of care (Samet et al., 2001). A study by Friedmann et al. (2006) found that onsite primary care in drug treatment programs reduced emergency department and hospital use among patients in methadone maintenance and long-term residential programs. Laine and colleagues (2001) retrospectively examined the association between outpatient medical and drug abuse care with later hospitalizations. Both HIV-seropositive and HIV-negative IDUs receiving regular medical and drug abuse care had the lowest adjusted odds ratio (AOR) for hospitalization (AOR=0.76; 95% CI: 0.67–0.85 and AOR=0.73; 95% CI: 0.68–0.79, respectively), compared with IDUs receiving one type of care (medical or drug abuse) or no care. Turner and colleagues (2003) found that among HIV-infected drug users, the odds of repeated emergency department visits were increased for those not receiving long-term drug treatment (methadone maintenance or drug-free treatment).

In another study, Friedmann and colleagues (2003) examined whether onsite primary care influenced addiction severity and medical outcomes. Findings showed that after 12 months, patients who attended programs with onsite primary care had lower addiction severity compared with patients attending programs with no primary care. There was no significant difference in medical outcomes.

Finally, Laine et al. (2005) examined the association of services in drug-treatment clinics with repeated emergency department use. Repeated visits to emergency departments were less likely when medical services were provided onsite in low- to moderate-volume treatment clinics. In the United States, a multi-site research demonstration project is currently examining programs integrating buprenorphine maintenance treatment into HIV care settings, as certified primary care physicians can now prescribe buprenorphine.

Because of the high prevalence of HIV among injecting drug users, researchers have examined whether directly administered antiretroviral therapy (DAART) provided at methadone clinics could improve treatment adherence and outcomes among HIV-seropositive IDUs. A study by Lucas et al. (2006) at a methadone clinic in Baltimore in the United States showed that after 12 months, DAART participants were significantly more likely to achieve viral suppression than HIV-seropositive IDU patients receiving methadone, IDUs not receiving methadone, and non-IDU patients. Antiretroviral therapy was available to all patients. The results also suggest that DAART was feasible and acceptable to patients in a methadone clinic

setting. Furthermore, DAART has proven quite inexpensive and feasible in low-resource settings (IOM, 2005). A study by Moatti and colleagues (2000) in France showed that active IDUs were some five times more likely to be non-adherent in their HIV treatment than IDUs on buprenorphine maintenance treatment and former IDUs. There was no significant difference between the adherence of IDUs on buprenorphine and former IDUs.

Another reason for more closely integrating ART and opioid agonist maintenance treatment is that the two sets of drugs often have serious interactions that require careful dose adjustments and monitoring. There is a significant literature documenting interactions between opioid agonist maintenance drugs and other drugs, particularly those involving metabolism by liver cytochrome P450 3A4 such as antiretroviral medications. Several studies have demonstrated that some of the drugs used to treat HIV and associated illnesses affect metabolism of opioid agonist maintenance medications (Iribarne et al., 1998; McCance-Katz et al., 2001, 2003, 2006). Some antiretroviral medications increase the metabolism of methadone, and initiation of treatment with these medications in methadone maintained patients may lead to withdrawal symptoms if the methadone dose is not increased (McCance-Katz et al., 2003, 2006). Other antiretrovirals may inhibit metabolism of methadone or buprenorphine and lead to increased levels of the maintenance medication (McCance-Katz et al., 2003, 2006); in this case, if patients experience sedation, the opioid maintenance medication dosage may need to be reduced slightly. Opioid agonist maintenance medications may also interfere with the metabolism of the antiretroviral medication, necessitating adjustments of the antiretroviral medication dosage (McCance-Katz et al., 2006). Given the high prevalence of HIV among IDUs, such interactions need to be taken into consideration and may require additional monitoring.

These findings indicate that IDUs can benefit from further integration of or referrals to primary care, HIV care, and other social services. The model combining DAART with opioid agonist therapy suggests that it is beneficial and should be studied further. WHO et al. (2004) suggests that a clear and coherent service plan is required to address the large scale of problems and resource constraints in many countries facing an IDU-driven HIV epidemic. They suggest broad community-based programs should be explored as one option.

Based on this evidence, the Committee concludes:

Conclusion 2-19: Drug treatment services are not always well integrated with other health and social programs for drug users. Modest evidence from studies in the United States shows that providing basic primary care services as part of drug treatment reduces emergency department use and hospitalization among

IDUs (which are indicators of poor access to or quality of care). Evidence also indicates that providing directly administered antiretroviral therapy to HIV-seropositive IDUs can improve adherence and treatment outcomes, but it is important to monitor potential drug interactions between antiretroviral medications and opioid agonist maintenance drugs. These findings indicate that IDUs can benefit from integrated drug treatment, HIV care, and other health and social services.

RECOMMENDATIONS

Based on its review of the evidence, the Committee makes the following recommendations:

Recommendation 2-1: Given the strong evidence of its effectiveness in treating opioid dependence, opioid agonist maintenance treatment should be made widely available where feasible. Such programs should include:

- **The necessary infrastructure to make treatment widely available (e.g., clinics, trained health workers) and a strategy to ensure sustainability.**
- **Assurance of adequate dosage and treatment duration.**
- **A balance between strategies to decrease diversion of treatment medication and strategies to disseminate the treatment.**
- **An evaluation component to monitor treatment implementation, quality, and outcomes.**
- **Monitoring of potential drug interactions between antiretroviral medications and opioid agonist maintenance drugs for HIV-infected IDUs.**

Recommendation 2-2: Given the potential benefits and lack of harmful effects, the following treatments should also be made available as part of a multi-component treatment system, where feasible, but should include a rigorous evaluation component:

- **Naltrexone treatment for opioid-dependent patients interested in abstinence-oriented treatment.**
- **Specific behavioral treatments (contingency management, cognitive behavioral therapy, community reinforcement approach, motivational interviewing, and individual drug counseling) for treating stimulant dependence.**
- **Chemical dependency treatment, therapeutic communities, and Drug Anonymous groups for patients dependent on any drug class who are interested in abstinence-oriented treatment.**

FUTURE RESEARCH

There is strong and consistent evidence that opioid agonist maintenance treatment reduces illicit opioid use and drug-related HIV risk factors, and modest evidence that such treatment protects against HIV infection. There is also strong evidence that higher doses of methadone and buprenorphine are more effective than lower doses in reducing illicit opioid use, and that longer duration of treatment is associated with greater treatment benefits. However, the optimal level of psychosocial interventions for patients receiving opioid agonist maintenance treatment, for patients with different treatment needs, and for reducing HIV risk behavior have not been established. These important areas require further research. While all opioid agonist medications used can be abused, research is also needed to evaluate the best strategies for reducing diversion and abuse while facilitating widespread coverage of patients in need of treatment. During the scaling up process for disseminating opioid agonist maintenance treatment and when opioid agonist maintenance treatment is widely available in a country, treatment outcomes are likely to vary across programs and sites and, within sites, among patients with differing characteristics. Health service delivery research can play an important role in identifying program characteristics or components associated with improved (or adverse) outcomes and also in identifying patient subgroups who respond well to standard interventions or who require additional treatments.

A variety of other approaches are often used to treat opioid dependence. However, the evidence regarding the efficacy and effectiveness of opioid antagonist maintenance treatment, specifically naltrexone, is weak to modest, and the evidence for psychosocial interventions alone in treating opioid dependence is weak. Little research has been done to evaluate the effectiveness of naltrexone treatment or psychosocial interventions alone for reducing HIV risk behavior or HIV transmission associated with opioid dependence. Nevertheless, some patients respond to these treatments, and some will not accept or cannot access opioid agonist maintenance treatment. These considerations support the importance of additional research aimed at identifying patient characteristics that could be used to predict good response to antagonist maintenance treatment or psychosocial treatments alone, or that could be used to improve the efficacy of these treatments.

Similar considerations apply to stimulant dependence, where there is an urgent need to develop and evaluate effective treatments. No pharmacological treatment has been consistently found efficacious in treating dependence on amphetamine-type stimulants. Strong evidence supports the efficacy of contingency management, but the feasibility and acceptability of this treatment in clinical practice settings is problematic. The evidence sup-

porting the efficacy of several other psychosocial treatments for stimulant dependence is modest. As with psychosocial treatments for opioid dependence, no studies have evaluated the effectiveness of psychosocial treatments other than contingency management for reducing HIV risk behavior or HIV transmission. Given the rising prevalence of amphetamine-type stimulant abuse worldwide, and its association with HIV transmission, studies of treatments for stimulant dependence are critical.

Recommendation 2-3: Given the relative weakness of the evidence, further research should occur on the following issues related to treatment for drug dependence:

- **The additional benefits and cost-effectiveness of adding psychosocial interventions to opioid agonist maintenance treatment for opiate-dependent people in high-risk countries, and the relative effectiveness of those interventions in particular cultural contexts and for particular patient subgroups.**
- **Pharmacotherapies for stimulant abuse, particularly amphetamine-type stimulants which have emerged as a major problem in many parts of the world.**
- **The effectiveness of naltrexone for different patient populations and in different settings.**
- **The relative effectiveness of various psychosocial interventions in treating opiate dependence in places where opioid agonist maintenance therapy is not available or accessible.**
- **Developing cost-effective and feasible alternatives to voucher-based contingency management approaches for treating stimulant dependence.**
- **Effective strategies for reducing sex-related risk behavior of IDUs in treatment.**
- **Optimal strategies for linking drug dependence treatment with health and social services.**

CONCLUSION

In this chapter, the Committee reviewed the evidence of effectiveness of drug dependence treatment in reducing drug-use, drug- and sex-related HIV risk behaviors, and HIV seroconversion. The Committee's findings and recommendations for policymakers and clinicians are summarized as follows:

For injecting opioid users seeking treatment: Opioid agonist maintenance treatment is the only consistently effective treatment for opioid dependence. Studies show that it reduces illicit opioid use, injection-related HIV risk

behaviors, and risk of HIV seroconversion among people with opioid dependence. Given the strong evidence of its effectiveness, opioid agonist maintenance treatment should be made widely available where feasible. The medication should be provided in sufficiently high doses and for a sufficient duration for therapeutic effects to occur. Programs should include adequate infrastructure, a plan for sustainability, and balance between strategies to decrease potential diversion and strategies to disseminate the treatment. Pharmacological treatments for opioid dependence do not have reliable or sustained effects on non-opiate use or on high-risk sexual behaviors. Clinicians and policymakers hoping to affect these behaviors will require other interventions and services to effect those changes.

Opioid antagonist medication is another pharmacological treatment option for opioid-dependent individuals who will not accept or cannot access opioid agonist maintenance therapy. Despite strong pharmacologic evidence and theoretical potential of naltrexone in blocking opiate effects, its efficacy in controlled clinical trials is inconclusive. Naltrexone is likely to be most successful for patients whose medication adherence and treatment retention can be closely monitored and facilitated. Additional research needs to be done regarding the effectiveness of naltrexone for different patient populations and in different settings.

Psychosocial interventions alone have not been shown to be consistently effective in treating opioid dependence. More research is needed on the additional benefits and cost-effectiveness of adding psychosocial interventions to opioid agonist maintenance treatment for opiate-dependent people in high-risk countries, and the relative effectiveness of those interventions in particular cultural contexts and for particular patient subgroups. More research is also needed on the relative effectiveness of various psychosocial interventions in treating opiate dependence in situations where opioid agonist maintenance therapy is not available.

For injecting non-opiate users seeking treatment: No pharmacotherapies have been found to be consistently efficacious in treating stimulant dependence. Contingency management is an efficacious treatment for stimulant dependence, but additional research is needed on the feasibility of its application outside of research settings. There is modest evidence of efficacy of other several behavioral or psychotherapeutic approaches in addressing stimulant abuse, including individual drug counseling and intensive group drug counseling, cognitive behavioral therapy, and community reinforcement combined with contingency management. Those seeking effective interventions for non-opioid users should consider behavioral or psychosocial interventions, but funders and policymakers are urged to collect rigorous evaluation data on those options if they are selected. Additional research should be done regarding pharmacotherapies for stimulant abuse,

particularly amphetamine-type stimulants, which have emerged as a major problem in many parts of the world. More research is also needed on developing cost-effective and feasible alternatives to voucher-based contingency management approaches for treating stimulant dependence outside of the research setting.

For injecting drug users not enrolled in treatment: The effectiveness of various strategies for drug users not in treatment, namely sterile syringe access programs and outreach and education, are discussed in Chapter 3.

Not all treatment options will work for all individuals. Specific treatments and their intensity, frequency, duration, and location would ideally be matched to the needs of individual patients. Patient-specific factors include the type and severity of abuse/addiction, co-occurring psychiatric or other drug disorders, co-morbid medical problems, treatment readiness and motivation, employment, family and social support, and involvement in the criminal justice system. These factors also affect treatment response, and studies need to evaluate whether differences in treatment outcomes result from differences in treatment or the characteristics of patients. Some studies suggest that matching specific treatment services to patients' needs improves outcomes (Carise et al., 2005; Gurel et al., 2005). While policymakers should invest resources in the most effective and cost-effective treatments, it is important to have a range of treatment options available.

REFERENCES

Abbott PJ, Weller S, Delaney H, Moore B. 1998. Community reinforcement approach in the treatment of opiate addicts. *American Journal of Drug and Alcohol Abuse*. 24(1):17–30.

Amato L, Minozzi S, Davoli M, Vecchi S, Ferri M, Mayet S. 2004. Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. *The Cochrane Database of Systematic Reviews*. (4):CD004147.

Anglin MD, Speckart GR, Booth MW, Ryan TM. 1989. Consequences and costs of shutting off methadone. *Addictive Behaviors*. 14(3):307–326.

Auriacombe M, Fatséas M, Dubernet J, Daulouède JP, Tignol J. 2004. French field experience with buprenorphine. *American Journal on Addictions*. 13:S17–S28.

Avants SK, Margolin A, Kosten TR, Rounsaville BJ, Schottenfeld RS. 1998. When is less treatment better? The role of social anxiety in matching methadone patients to psychosocial treatments. *Journal of Consulting and Clinical Psychology*. 66(60):924–931.

Avants SK, Margolin A, Sindelar JL, Rounsaville BJ, Schottenfeld R, Stine S, Cooney NL, Rosenheck RA, Li SH, Kosten TR. 1999. Day treatment versus enhanced standard methadone services for opioid-dependent patients: A comparison of clinical efficacy and cost. *American Journal of Psychiatry*. 156(1):27–33.

Avants SK, Margolin A, Usubiaga MH, Doebrick C. 2004. Targeting HIV-related outcomes with intravenous drug users maintained on methadone: A randomized clinical trial of a harm reduction group therapy. *Journal of Substance Abuse Treatment*. 26:67–78.

Backmund M, Schutz CH, Meyer K, Eichenlaub D, Soyka M. 2003. Alcohol consumption in heroin users, methadone-substituted and codeine-substituted patients-frequency and correlates of use. *European Addiction Research*. 9:45–50.

Baker A, Heather N, Wodak A, Dixon J, Holt P. 1993. Evaluation of a cognitive-behavioural intervention for HIV prevention among injecting drug users. *AIDS*. 7(2):247–256.

Baker A, Kochan N, Dixon J, Wodak A, Heather N. 1995. HIV risk-taking behaviour among injecting drug users currently, previously and never enrolled in methadone treatment. *Addiction*. 90:545–554.

Bale RN, Van Stone WW, Kuldau JM, Engelsing TM, Elashoff RM, Zarcone VP Jr. 1980. Therapeutic communities vs methadone maintenance. A prospective controlled study of narcotic addiction treatment: Design and one-year follow-up. *Archives of General Psychiatry*. 37(2):179–193.

Bandura, A. 1994. Self-efficacy. In Ramachaudran VS, ed., *Encyclopedia of Human Behavior* Volume 4, pp. 71–81. New York: Academic Press. Reprinted in Friedman H, ed., 1998. *Encyclopedia of Mental Health*. San Diego: Academic Press.

Batki SL, Sorenson JL, Gibson DR, Maude-Griffin P. 1989. HIV-infected IV drug users in methadone treatment: Outcome and psychological correlates—a preliminary report. *NIDA Research Monograph Series*. 95:405–406.

Berson A, Gervais A, Cazals D, Boyer N, Durand F, Bernuau J, Marcellin P, Pegott C, Valla D, Pessayre D. 2001. Hepatitis after intravenous buprenorphine misuse in heroin addicts. *Journal of Hepatology*. 34:346–350.

Britton BM. 1994. The privatization of methadone maintenance: Changes in risk behavior associated with cost related detoxification. *Addiction Research*. 2(2):171–181.

Brooner R, Kidorf M, King V, Beilenson P, Svikis D, Vlahov D. 1998. Drug abuse treatment success among needle exchange participants. *Public Health Reports*. 113:483–489.

Burke BL, Arkowitz H, Menchola M. 2003. The efficacy of motivational interviewing: A meta-analysis of controlled clinical trials. *Journal of Consulting and Clinical Psychology*. 71:843–861.

Camacho LM, Barthoomew NG, Joe GW, Cloud MA, Simpson DD. 1996. Gender, cocaine and during-treatment HIV risk reduction among injection opioid users in methadone maintenance. *Drug and Alcohol Dependence*. 41:1–7.

Caplehorn JR, Dalton MS, Cluff MC, Petrenas AM. 1994. Retention in methadone maintenance and heroin addicts' risk of death. *Addiction*. 89(2):203–209.

Carise D, Gurel O, McLellan AT, Dugosh K, Kendig C. 2005. Getting patients the services they need using a computer-assisted system for patient assessment and referral—CASPAR. *Drug and Alcohol Dependence*. 80(2):177–189.

Carrieri MP, Rey D, Loundou A, Lepeu G, Sobel A, Obadia Y. 2003. Evaluation of buprenorphine maintenance treatment in a French cohort of HIV-infected injecting drug users. *Drug and Alcohol Dependence*. 72(1):13–21.

Carroll, KM, Rounsaville BJ, Gordon LT, Nich C, Jatlow PM, Bisighini RM, Gawin FH. 1994. One year follow-up of psychotherapy and pharmacotherapy for cocaine dependence: Delayed emergence of psychotherapy effects. *Archives of General Psychiatry*. 51(12):989–997.

Carroll KM, Nich C, Ball SA, McCance-Katz E, Rounsaville BJ. 1998. Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram. *Addiction*. 93:713–728.

Carroll KM, Nich C, Ball SA, McCance-Katz ER, Frankforter TF, Rounsaville BJ. 2000. One-year follow-up of disulfiram and psychotherapy for cocaine-alcohol abusers: Sustained effects of treatment. *Addiction*. 95:1335–1349.

Carroll KM, Sinha R, Nich C, Babuscio T, Rounsaville BJ. 2002. Contingency management to enhance naltrexone treatment of opioid dependence: A randomized clinical trial. *Experimental and Clinical Pharmacology*. 10(1):54–63.

Carroll KM, Renton LR, Ball SA, Nich C, Frankforter TL, Shi J, Rounsaville BJ. 2004. Efficacy of disulfiram and cognitive behavior therapy in cocaine-dependent outpatients: A randomized placebo-control trial. *Archives of General Psychiatry*. 61:264–272.

Chatham LR, Hiller ML, Rowan-Szal GA, Joe GW, Simpson DD. 1999. Gender differences at admission and follow-up in a sample of methadone maintenance clients. *Substance Use and Misuse*. 34(8):1137–1165.

Chick J. 1999. Safety issues concerning the use of disulfiram in treating alcohol dependence. *Drug Safety*. 20(5): 427–435.

Cicero TJ, Inciardi JA. 2005. Diversion and abuse of methadone prescribed for pain management. *Journal of the American Medical Association*. 293(3):297–298.

Clark N, Lintzeris N, Gijsbers A, Whelan G, Dunlop A, Ritter A, Ling W. 2002. LAAM maintenance vs methadone maintenance for heroin dependence. *The Cochrane Database of Systematic Reviews*. (2):CD002210.

Colfax G, Shoptaw S. 2005. The methamphetamine epidemic: Implications for HIV prevention and treatment. *Current HIV/AIDS Reports*. 2:194–199.

Comer SD, Collins ED. 2002. Self-administration of intravenous buprenorphine and the buprenorphine/naloxone combination by recently detoxified heroin abusers. *Journal of Pharmacology and Experimental Therapeutics*. 303(2):695–703.

Cornish JW, Metzger D, Woody GE, Wilson D, McLellan AT, Vandergrift B, O'Brien CP. 1997. Naltrexone pharmacotherapy for opioid dependent federal probationers. *Journal of Substance Abuse Treatment*. 14(6):529–534.

Courtnage PA. 1991. HIV/AIDS risk reduction through treatment of cocaine-dependent methadone patients: A multiaxial intervention. *Dissertation Abstracts International*. 52(11B), 0630.

Crits-Christoph P, Siqueland L, Blaine J, Frank A, Luborsky L, Onken LS, Muenz LR, Thase ME, Weiss RD, Gastfriend DR, Woody GE, Barber JP, Butler SF, Daley D, Salloum I, Biship S, Najavits LM, Lis J, Mercer D, Griffin ML, Moras K, Beck AT. 1999. Psychosocial treatments for cocaine dependence. *Archives of General Psychiatry*. 56:493–502.

Curran S, Savage C. 1976. Patient response to naltrexone: Issues of acceptance, treatment effects, and frequency of administration. *NIDA Research Monograph*. (9):67–69.

Darke SG, Ross JE, Hall WD. 1995. Benzodiazepine use among injecting heroin users. *The Medical Journal of Australia*. 162(12):645–647.

Digiusto E, Shakeshaft A, Ritter A, O'Brien S, Mattick RP; The NEPOD Research Group. 2004. Serious adverse events in the Australian National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD). *Addiction*. 99:450–460.

Dolan KA, Shearer J, MacDonald M, Mattick RP, Hall W, Wodak AD. 2003. A randomized controlled trial of methadone maintenance treatment versus wait list control in an Australian prison system. *Drug and Alcohol Dependence*. 72:59–65.

Dole VP, Robinson JW, Orraca J, Towns E, Searcy P, Caine E. 1969. Methadone treatment of randomly selected criminal addicts. *New England Journal of Medicine*. 280(25):1372–1375.

Dunbar JL, Turncliff RZ, Dong Q, Silverman BL, Ehrich EW, Lasseter KC. 2006. Single- and multiple-dose pharmacokinetics of long-acting injectable naltrexone. *Alcoholism, Experimental and Clinical Research*. 30(3):480–490.

Elkader A, Sproule B. 2005. Buprenorphine: Clinical pharmacokinetics in the treatment of opioid dependence. *Clinical Pharmacokinetics*. 44(7):661–680.

EMEA (European Agency for the Evaluation of Medicinal Products). 2001. *EMEA Public Statement on the Recommendation to Suspend Marketing Authorization for ORLAAM (levacetylmethadol) in the European Union*. [Online]. Available: http://www.emea.eu.int/pdfs/human/press/pus/877601en.pdf [accessed June 30, 2006].

Enghusen Poulsen H, Loft S, Andersen JR, Andersen M. 1992. Disulfiram therapy—adverse drug reactions and interactions. *Acta Psychiatrica Scandinavica Suppl. 369*:59–65.

Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. 2003. Methadone maintenance at different dosages for opioid dependence. *The Cochrane Database of Systematic Reviews*. (3):CD002208.

Fairbank JA, Dunteman GH, Condelli WS. 1993. Do methadone patients substitute other drugs for heroin? Predicting substance use at 1-year follow-up. *American Journal of Drug and Alcohol Abuse*. 19(4):465–474.

Frank B, Galea J. 1996. Cocaine trends and other drug trends in New York City, 1986-1994. *Journal of Addictive Diseases*. 15:1–12

Friedmann PD, Zhang Z, Hendrickson J, Stein MD, Gerstein DR. 2003. Effect of primary medical care on addiction and medical severity in substance abuse treatment programs. *Journal of General Internal Medicine*. 18:1–8.

Friedmann PD, Hendrickson JC, Gerstein DR, Zhang Z, Stein MD. 2006. Do mechanisms that link addiction treatment patients to primary care influence subsequent utilization of emergency and hospital care? *Medical Care*. 44(1):8–15.

Fudala PJ, Bridge TP, Herbert S, Williford WO, Chiang CN, Jones K, Collins J, Raisch D, Casadonte P, Goldsmith RJ, Ling W, Malkerneker U, McNicholas L, Renner J, Stine S, Tusel D; Buprenorphine/Naloxone Collaborative Study Group. 2003. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *New England Journal of Medicine*. 349(10):949–958.

Fugelstad A, Rajs J, Bottiger M, de Verdier MG. 1995. Mortality among HIV-infected intravenous drug addicts in Stockholm in relation to methadone treatment. *Addiction*. 90:711–716.

Fugelstad A, Annell A, Rajs J, Agren G. 1997. Mortality and causes and manner of death among drug addicts in Stockholm during the period 1981–1992. *Acta Psychiatrica Scandinavica*. 96:169–175.

Fugelstad A, Agren G, Romelsjo A. 1998. Changes in mortality, arrests, and hospitalizations in nonvoluntarily treated heroin addicts in relation to methadone treatment. *Substance Use & Misuse*. 33(14):2803–2817.

George TP, Chawarski MC, Pakes JA, Carroll KM, Kosten TR, Schottenfeld RS. 2000. Disulfiram versus placebo for cocaine dependence in buprenorphine-maintained subjects: A preliminary trial. *Biological Psychiatry*. 47:1080–1086.

Gibson DR, McCusker J, Chesney M. 1998. Effectiveness of psychosocial interventions in preventing HIV risk behaviour in injecting drug users. *AIDS*. 12(8):919–929.

Gossop M, Marsden J, Steward D, Rolfe A. 2000. Patterns of improvement after methadone treatment: 1 year follow-up results from the National Treatment Outcome Research Study (NTORS). *Drug Alcohol Dependency*. 60:275–286.

Gouny P, Gaitz JP, Vayssairat M. 1999. Acute hand ischemia secondary to intra-arterial buprenorphine injection: Treatment with iloprost and dextran-40—a case report. *Angiology*. 50:605–606.

Gowing LR, Farrell M, Bornemann R, Ali R. 2004. Substitution treatment of injecting opioid users for prevention of HIV infection. *The Cochrane Database of Systematic Reviews*. (4):CD004145.

Gowing LR, Farrell M, Bornemann R, Sullivan LE, Ali RL. 2005. Brief report: Methadone treatment of injecting opioid users for prevention of HIV infection. *Journal of General Internal Medicine*. 20:1–3.

GRADE Working Group. 2004. Grading quality of evidence and strength of recommendation. *British Medical Journal*. 328:1490–1498.

Grella CE, Anglin MD, Wugalter SE. 1995. Cocaine and crack use and HIV risk behaviors among high-risk methadone maintenance clients. *Drug and Alcohol Dependence*. 37: 15–21.

Grella CE, Anglin MD, Annon JJ. 1996. HIV risk behaviors among women in methadone maintenance treatment. *Substance Use and Misuse*. 31(3):277–301.

Grella CE, Anglin MD, Wugalter SE. 1997. Patterns and predictors of cocaine and crack use by clients in standard and enhanced methadone maintenance treatment. *American Journal of Drug and Alcohol Abuse*. 23:15–42.

Guichard A, Lert F, Calderon C, Gaigi H, Maguet O, Soletti J, Brodeur JM, Richard L, Benigeri M, Zunzunegui MV. 2003. Illicit drug use and injection practices among drug users on methadone and buprenorphine maintenance treatment in France. *Addiction*. 98(11):1585–1597.

Gunne LM, Gronbladh L. 1981. The Swedish methadone maintenance program: A controlled study. *Drug and Alcohol Dependence*. 7(3):249–256.

Guo S, Jiang Z, Wu Y. 2001. Efficacy of naltrexone hydrochloride for preventing relapse among opiate-dependent patients after detoxification. *Hong Kong Journal of Psychiatry*. 11(4):2–8.

Gurel O, Carise D, Kendig C, McLellan AT. 2005. Developing CASPAR: A computer-assisted system for patient assessment and referral. *Journal of Substance Abuse Treatment*. (3):281–289.

Haisin DS, Grant BF, Endicott J, Hartford TC. 1988. Cocaine and heroin dependence compared in polydrug abusers. *American Journal of Public Health*. 8:567–569.

Harris RM, Bausell RB, Scott DE, Hetherington SE, Kavanagh KH. 1998. An intervention for changing high-risk HIV behaviors of African-American, drug dependent women. *Research in Nursing and Health*. 21:239–250.

Hartgers C, van den Hoek A, Krijnen P, Coutinho RA. 1992. HIV prevalence and risk behavior among injecting drug users who participate in "low-threshold" methadone programs in Amsterdam. *American Journal of Public Health*. 82(4):547–551.

Heinemann A, Iwersen-Bergmann S, Stein S, Schmoldt A, Puschel K. 2000. Methadone-related fatalities in Hamburg 1990–1999: Implications for quality standards in maintenance treatment? *Forensic Science International*. 113:449–455.

Higgins ST, Budney AJ, Bickel WK, Hughes JR, Foerg F, Fenwick W. 1991. A behavioral approach to achieving initial cocaine abstinence. *American Journal of Psychiatry*. 148:1218–1224.

Higgins ST, Budney AJ, Bickel WK, Hughes JR, Foerg F, Badger G. 1993. Achieving cocaine abstinence with a behavioral approach. *American Journal of Psychiatry*. 150:763–769.

Higgins ST, Budney AJ, Bickel WK, Foerg FE, Donham R, Badger GJ. 1994. Incentives improve outcome in outpatient behavioral treatment of cocaine dependence. *Archives of General Psychiatry*. 51:568–576.

Higgins ST, Wong CJ, Badger GJ, Ogden DE, Dantona RL. 2000. Contingent reinforcement increases cocaine abstinence during outpatient treatment and 1 year of follow-up. *Journal of Consulting and Clinical Psychology*. 68:64–72.

Higgins ST, Sigmon SC, Wong CJ, Heil SH, Badger GJ, Donham R, Dantona RL, Anthony S. 2003. Community reinforcement therapy for cocaine dependent outpatients. *Archives of General Psychiatry*. 60(10):1043–1052.

Hill AB. 1961. *Principles of Medical Statistics*. New York: Oxford University Press.

Hollister LE. 1978. Clinical evaluation of naltrexone treatment of opiate-dependent individuals. Report of the National Research Council Committee on Clinical Evaluation of Narcotic Antagonists. *Archives of General Psychiatry*. 35(3):335–340.

Hopwood M, Southgate E, Kippax S, Bammer G, Isaac-Toua G, MacDonald M. 2003. The injection of methadone syrup in New South Wales: Patterns of use and increased harm after partial banning of injecting equipment. *Australian and New Zealand Journal of Public Health*. 27:551–555.

Hser YI, Hoffman V, Grella CE, Anglin MD. 2001. A 33-year follow-up of narcotics addicts. *Archives of General Psychiatry*. 58(5):503–508.

Hubbard RL, Craddock SG, Anderson J. 2003. Overview of 5-year follow-up outcomes in the drug abuse treatment outcome studies (DATOS). *Journal of Substance Abuse Treatment*. 25:125–134.

IOM (Institute of Medicine). 1990. *Treating Drug Problems: Volume 1*. Washington, DC: National Academy Press.

IOM. 1995. *Federal Regulation of Methadone Treatment*. Washington, DC: National Academy Press.

IOM. 2005. *Scaling Up Treatment for the Global AIDS Pandemic*. Washington, DC: The National Academies Press.

Iribarne C, Berthou F, Carlhant D, Dreano Y, Picart D, Lohezic F, Riche C. 1998. Inhibition of methadone and buprenorphine N-dealkylations by three HIV-1 protease inhibitors. *Drug Metabolism and Disposition*. 26(3):257–260.

Johansson BA, Berglund M, Lindgren A. 2006. Efficacy of maintenance treatment with naltrexone for opioid dependence: A meta-analytical review. *Addiction*. 101:491–503.

Johnson RE, Eissenberg T, Stitzer ML, Strain EC, Liebson IA, Bigelow GE. 1995. A placebo controlled clinical trial of buprenorphine as a treatment for opioid dependence. *Drug and Alcohol Dependence*. 40(1):17–25.

Kakko J, Svanborg KD, Kreek MJ, Heilig M. 2003. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: A randomised, placebo-controlled trial. *Lancet*. 361(9358):662–668.

Katz EC, Chutuape MA, Jones HE, Stitzer ML. 2002. Voucher reinforcement for heroin and cocaine abstinence in an outpatient drug-free program. *Experimental and Clinical Pharmacology*. 10(2):136–143.

King VL, Kidorf MS, Stoller KB, Brooner RK. 2000. Influence of psychiatric comorbidity on HIV risk behaviors: Changes during drug abuse treatment. *Journal of Addictive Diseases*. 19:65–83.

Kintz P. 2001. Deaths involving buprenorphine: A compendium of French cases. *Forensic Science International*. 121:6–69.

Kirchmayer U, Davoli M, Verster A. 2003. Naltrexone maintenance treatment for opioid dependence. *The Cochrane Database of Systematic Reviews*. (2):CD001333.

Kosten TR, Rounsaville BJ, Kleber HD. 1987. A 2.5-year follow-up of cocaine use among treated opioid addicts. Have our treatments helped? *Archives of General Psychiatry*. 44:281–284.

Kosten TR, Rounsaville BJ, Kleber HD. 1988. Antecedents and consequences of cocaine abuse among opioid addicts. A 2.5-year follow-up. *Journal of Nervous and Mental Disorders*. 176(3):176–181.

Kosten TR, Krystal JH, Charney DS, Price LH, Morgan CH, Kleber HD. 1990. Opioid antagonist challenges in buprenorphine maintained patients. *Drug and Alcohol Dependence* 25(1):73–78.

Krook AL, Brors O, Dahlberg J, Grouff K, Magnus P, Roysamb E, Waal H. 2002. A placebo-controlled study of high dose buprenorphine in opiate dependents waiting for medication-assisted rehabilitation in Oslo, Norway. *Addiction*. 97(5):533–542.

Krupitsky EM, Zvartau EE, Masalov DV, Tsoi MV, Burakov AM, Egorova VY, Didenko TY, Romanova TN, Ivanova EB, Bespalov AY, Verbitskaya EV, Neznanov NG, Grinenko AY, O'Brien CP, Woody GE. 2004. Naltrexone for heroin dependence treatment in St. Petersburg, Russia. *Journal of Substance Abuse Treatment*. 26:285–294.

Krupitsky EM, Zvartau EE, Masalov DV, Tsoy MV, Burakov AM, Egorova VY, Didenko TY, Romanova TN, Ivanova EB, Bespalov AY, Verbitskaya EV, Neznanov NG, Grinenko AY, O'Brien CP, Woody GE. 2006. Naltrexone with or without fluoxetine for preventing relapse to heroin addiction in St. Petersburg, Russia. *Journal of Substance Abuse Treatment*. In press, corrected proof. [Available online July 24, 2006].

Kwiatkowski CF, Booth RE. 2001. Methadone maintenance as HIV risk reduction with street-recruited injecting drug users. *Journal of Acquired Immune Deficiencies Syndromes*. 26(5):483–489.

Ladewig D. 1990. Naltrexone—an effective aid in the psychosocial rehabilitation process of former opiate dependent patients. *Therapeutische Umschau*. 47(3):247–250.

Laine C, Hauck WW, Gourevitch, Rothman J, Cohen A, Turner BJ. 2001. Regular outpatient medical and drug abuse care and subsequent hospitalization of persons who use illicit drugs. *Journal of the American Medical Association*. 285(18):2355–2362.

Laine C, Lin YT, Hauck WW, Turner BJ. 2005. Availability of medical care services in drug treatment clinics associated with lower repeated emergency department use. *Medical Care*. 43(10):985–995.

Last J. 1995. *A Dictionary of Epidemiology. 3rd edition*. New York: Oxford University Press.

Leri F, Bruneau J, Stewart J. 2003. Understanding polydrug use: Review of heroin and cocaine co-use. *Addiction*. 98:7–22.

Lerner A, Sigal M, Bacalu A, Shiff R, Burganski I, Gelkopf M. 1992. A naltrexone double-blind placebo controlled study in Israel. *Israel Journal of Psychiatry and Related Sciences*. 29(1):36–43.

Lima MS, Reisser Lima AAP, Soares BGO, Farrell M. 2003. Antidepressants for cocaine dependence. *The Cochrane Database of Systematic Reviews*. (2):CD002950.

Lima Reisser A, Lima MS, Soares BGO, Farrell M. 2002. Carbamazepine for cocaine dependence. *The Cochrane Database of Systematic Reviews*. (2):CD002023.

Ling W, Charuvastra C, Collins JF, Batki S, Brown Jr. LS, Kintaudi P, Wesson DR, McNicholas L, Tusel DJ, Malkerneker U, Renner Jr. JA, Santos E, Casadonte P, Fye C, Stine S, Wang RIH, Segal D. 1998. Buprenorphine maintenance treatment of opiate dependence: A multicenter, randomized clinical trial. *Addiction*. 93(4):475–486.

Lintzeris N, Lenne M, Ritter A. 1999. Methadone injecting in Australia: A tale of two cities. *Addiction*. 94:1175–1178.

Lucas GM, Mullen BA, Weidle PJ, Hader S, MCaul ME, Moore RD. 2006. Directly administered antiretroviral therapy in methadone clinics is associated with improved HIV treatment outcomes, compared with outcomes among concurrent comparison groups. *Clinical Infectious Diseases*. 42:1628–1635.

MacCoun R, Reuter P. 2001. *Drug War Heresies: Learning from Other Vices, Times, and Places*. Cambridge, UK: Cambridge University Press.

Maddux JF, Desmond DP. 1997. Outcomes of methadone maintenance 1 year after admission. *Journal of Drug Issues*. 27(2):225–238.

Magura S, Siddiqi Q, Shapiro J, Grossman JI, Lipton DS, Marion IJ, Weisenfeld L, Amann KR, Koger J. 1991. Outcomes of an AIDS prevention program for methadone patients. *International Journal of Addiction*. 26(6):629–655.

Magura S, Kang SY, Nwakeze PC, Demsky S. 1998. Temporal patterns of heroin and cocaine use among methadone patients. *Substance Use and Misuse*. 33(12):2441–2467.

Margolin A, Avants SK, Warburton LA, Hawkins KA, Shi J. 2003. A randomized clinical trial of a manual-guided risk reduction intervention for HIV-positive injection drug users. *Health Psychology*. 22(2):223–228.

Mattick RP, Breen C, Kimber J, Davoli M. 2003a. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *The Cochrane Database of Systematic Reviews*. (2):CD002209.

Mattick RP, Kimber J, Davoli M. 2003b. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *The Cochrane Database of Systematic Reviews*. (2):CD002207.

Maude-Griffin PM, Hohenstein JM, Humfleet GL, Reilly PM, Tusel DJ, Hall SM. 1998. Superior efficacy of cognitive-behavioral therapy for crack cocaine abusers: Main and matching effects. *Journal of Consulting and Clinical Psychology*. 66:832–837.

Mayet S, Farrell M, Ferri M, Amato L, Davoli M. 2004. Psychosocial treatment for opiate abuse and dependence. *The Cochrane Database of Systematic Reviews*. (4):CD004330.

McCance-Katz EF, Rainey PM, Friedland G, Kosten TR, Jatlow P. 2001. Effect of opioid dependence pharmacotherapies on zidovudine disposition. *American Journal of Addictions*. 10(4):296–307.

McCance-Katz EF, Rainey PM, Friedland G, Jatlow P. 2003. The protease inhibitor lopinavir-ritonavir may produce opiate withdrawal in methadone-maintained patients. *Clinical Infectious Diseases*. 37(4):476–482.

McCance-Katz EF, Rainey PM, Smith P, Morse GD, Friedland G, Boyarsky B, Gourevitch M, Jatlow P. 2006. Drug interactions between opioids and antiretroviral medications: Interaction between methadone, LAAM, and delavirdine. *American Journal on Addictions*. 15(1):23–34.

McGlothin WH, Anglin MD. 1981. Shutting off methadone: costs and benefits. *Archives of General Psychiatry*. 38:885–892.

McKay JR, Alterman AI, Cacciola JS, Rutherford MJ, O'Brien CP, Koppenhaver J. 1997. Group counseling versus individualized relapse prevention aftercare following intensive outpatient treatment for cocaine dependence. *Journal of Consulting and Clinical Psychology*. 65:778–788.

McLellan AT, Arndt IO, Metzger DS, Woody GE, O'Brien CP. 1993. The effects of psychosocial services in substance abuse treatment. *Journal of the American Medical Association*. 269(15):1953–1959.

Meandzija B, O'Connor PG, Fitzgerald B, Rounsaville BJ, Kosten TR. 1994. HIV infection and cocaine use in methadone maintained and untreated intravenous drug users. *Drug and Alcohol Dependence*. 36:109–113.

Mendelson J, Jones RT, Welm S, Baggott M, Fernandez I, Melby AK, Nath RP. 1999. Buprenorphine and naloxone combinations: The effects of three dose ratios in morphine-stabilized, opiate-dependent volunteers. *Psychopharmacology*. 141(1):37–46.

Metzger DS, Woody GE, McLellan AT, O'Brien CP, Druley P, Navaline H, DePhilippis D, Stolley P, Abrutyn E. 1993. Human immunodeficiency virus seroconversion among intravenous drug users in- and out-of-treatment: An 18-month prospective follow-up. *Journal of Acquired Immune Deficiency Syndromes*. 6(9):1049–1056.

Miller WR, Rollnick S. 1992. *Motivational Interviewing: Preparing People to Change Addictive Behavior*. New York: Guilford Press.

Minozzi S, Amato L, Vecchi S, Davoi M, Kirchmayer U, Verster A. 2006. Oral naltrexone maintenance treatment for opioid dependence. *The Cochrane Database of Systematic Reviews*. (1):CD001333.

Moatti JP, Carrieri MP, Spire B, Gastaut JA, Cassuto JP, Moreau J, Manif 2000 study group. 2000. Adherence to HAART in French HIV-infected injecting drugs users: The contribution of buprenorphine drug maintenance treatment. *AIDS*. 14(2):151–155.

Monti PM, Rohsenow DJ, Michalec E, Martin RA, Abrams DB. 1997. Brief coping skills treatment for cocaine abuse: Substance abuse outcomes at three months. *Addiction.* 92:1717–1728.

Moss AR, Vranizan K, Gorter R, Bacchetti P, Watters J, Osmond D. 1994. HIV seroconversion in intravenous drug users in San Francisco, 1985–1990. *AIDS.* 8(2):223–231.

Newman RG, Whitehill WB. 1979. Double-blind comparison of methadone and placebo maintenance treatments of narcotic addicts in Hong Kong. *Lancet.* 2(8141):485–488.

Nich C, Carroll KM. 2002. "Intention-to-treat" meets "missing data": Implications of alternate strategies for analyzing clinical trials data. *Drug and Alcohol Dependence.* 68: 121–130.

Obadia Y, Perrin V, Feroni I, Vlahov D, Moatti JP . 2001. Injecting misuse of buprenorphine among French drug users. *Addiction.* 96(2):267–272.

O'Brien C, Kampman K. 2004. Opioids: Antagonists and partial agonists. In: *The American Psychiatric Association Textbook of Substance Abuse Treatment.* 3rd edition. Washington, DC: American Psychiatric Press, Inc. Pp. 305–319.

O'Farrell TJ, Fals-Stewart W. 2002. Behavioral couples and family therapy for substance abusers. *Current Psychiatry Reports.* 4(5):371–376.

O'Malley SS, Jaffe AJ, Chang G, Rode S, Schottenfeld R, Meyer RE, Rounsaville B. 1996. Six month follow-up of naltrexone and psychotherapy for alcohol dependence. *Archives of General Psychiatry.* 53:217–224.

Peirce JM, Petry NM, Stitzer ML, Blaine J, Kellogg S, Satterfield F, Schwartz M, Krasnansky J, Pencer E, Silva-Vazquez L, Kirby KC, Royer-Malvestuto C, Roll JM, Cohen A, Copersino ML, Kolodner K, Li R. 2006. Effects of lower-cost incentives on stimulant abstinence in methadone maintenance treatment: A national drug abuse treatment clinical trials network study. *Archives of General Psychiatry.* 63(2):201–208.

Petrakis IL, Carroll KM, Gordon LT, Nich C, McCance-Katz E, Rounsaville BJ. 2000. Disulfiram treatment for cocaine dependence in methadone-maintained opioid addicts. *Addiction.* 95:219–228.

Petry NM, Martin B. 2002. Low-cost contingency management for treating cocaine- and opioid-abusing methadone patients. *Journal of Consulting and Clinical Psychology.* 70:398–405.

Petry NM, Tedford J, Austin M, Nich C, Carroll KM, Rounsaville BJ. 2004. Prize reinforcement contingency management for treating cocaine users: How low can we go, and with whom? *Addiction.* 99:349–360.

Piotrowski NA, Tusel DJ, Sees KL, Reilly PM, Banys P, Meek P, Hall SM. 1999. Contingency contracting with monetary reinforcers for abstinence from multiple drugs in a methadone program. *Experimental and Clinical Psychopharmacology.* 7(4):399–411.

Prendergast ML, Urada D, Podus D. 2001. Meta-analysis of HIV risk reduction interventions with drug abuse treatment programs. *Journal of Consulting and Clinical Psychology.* 69(3):389–405.

Project MATCH Research Group. 1998. Matching alcoholism treatments to patient heterogeneity: Treatment main effects and matching effects on drinking during treatment. *Journal of Studies on Alcohol.* 59:631–639.

Rawson RA, Glazer M, Callahan EJ, Liberman RP. 1979. Naltrexone and behaviour therapy for heroin addiction. *NIDA Research Monograph Series.* 25:26–43.

Rawson RA, Gonzales R, Brethen P. 2002. Treatment of methamphetamine use disorders: An update. *Journal of Substance Abuse Treatment.* 23:145–150.

Rawson RA, Marinelli-Casey P, Anglin MD, Dickow A, Frazier Y, Gallagher C, Galloway GP, Herrell J, Huber A, MacCann MJ, Obert J, Pennell S, Reiber C, Vandersloot D, Zweben J; Methamphetamine Treatment Project Corporate Authors. 2004. A multi-site comparison of psychosocial approaches for the treatment of methamphetamine dependence. *Addiction*. 99:708–717.

Reid G, Kamarulzaman, Sran SK. 2005. *Rapid Situational Assessment of Malaysia*. [Online]. Available: http://chr.asn.au/freestyler/gui/files//Rapid%20Situation%20Assessment%20of%20Malaysia1.pdf [accessed June 28, 2006].

Reynaud M, Petit G, Potard D, Couty P. 1998. Six deaths linked to concomitant use of buprenorphine and benzodiazepines. *Addiction*. 93:1385–1392.

Ritter A, Di Natale R. 2005. The relationship between take-away methadone policies and methadone diversion. *Drug and Alcohol Review*. 24:347–352.

Rohsenow DJ, Monti PM, Martin RA, Colby SM, Myers MG, Gulliver SB, Brown RA, Mueller TI, Gordon A, Abrams DB. 2004. Motivational enhancement and coping skills training for cocaine abusers: Effects on substance use outcomes. *Addiction*. 99(7): 862–874.

Rooney S, Kelly G, Bamford L, Sloan D, O'Connor JJ. 1999. Co-abuse of opiates and benzodiazepines. *Irish Journal of Medical Science*. 168(1):36–41.

Roozen HG, Boulogne JJ, van Tulder MW, van den Brink W, De Jong CAJ, Kerkhof AJFM. 2004. A systematic review of the effectiveness of the community reinforcement approach in alcohol, cocaine and opioid addiction. *Drug and Alcohol Dependence*. 74:1–13.

Rothbard A, Alterman A, Rutherford M, Liu F, Zelinski S, McKay J. 1999. Revisiting the effectiveness of methadone treatment on crime reductions in the 1990s. *Journal of Substance Abuse Treatment*. 16(4):329–335.

Roxanne Laboratories, Inc. 2003. *Product Discontinuation Notice. ORLAAM ® (Levomethadyl hydrochloride acetate) Oral Solution, 10 mg/mL, CII*. [Online]. Available: http://www.fda.gov/cder/drug/shortages/orlaam.htm [accessed August 28, 2006].

Samet JH, Friedmann P, Saitz R. 2001. Benefits of linking primary medical care and substance abuse services: Patient, provider, and societal perspectives. *Archives of Internal Medicine*. 161:85–91.

San L, Pomarol G, Peri JM, Olle JM, Cami J. 1991. Follow-up after a six-month maintenance period on naltrexone versus placebo in heroin addicts. *British Journal of Addiction*. 86(8):983–990.

Schilling RF, El-Bassel N, Schinke SP, Gordon K, Nichols S. 1991. Building skills of recovering women drug users to reduce heterosexual AIDS transmission. *Public Health Reports*. 106:297–304.

Schottenfeld RS. 2004. Opioids: Maintenance treatment. *The American Psychiatric Publishing Textbook of Substance Abuse Treatment*. 3rd edition. Galanter M, Kleber H, eds. Washington, DC: American Psychiatric Publishing, Inc.

Schottenfeld RS, Pakes J, Ziedonis D, Kosten TR. 1993. Buprenorphine: Dose-related effects on cocaine and opioid use in cocaine-abusing opioid-dependent humans. *Biological Psychiatry*. 34(1–2):66–74.

Schottenfeld RS, Pakes J, Oliveto A, Ziedonis D, Kosten TR. 1997. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Archives of General Psychiatry*. 54:713–720.

Schottenfeld RS, Chawarski MC, Pakes JR, Pantalon MV, Carroll KM, Kosten TR. 2005. Methadone versus buprenorphine with contingency management or performance feedback for cocaine and opioid dependence. *American Journal of Psychiatry*. 162(2): 340–349.

Schutz CG, Vlahov D, Anthony JC, Graham NM. 1994. Comparison of self-reported injection frequencies for past 30 days and 6 months among intravenous drug users. *Journal of Clinical Epidemiology*. 47:191–195.

Schwartz RP, Highfield DA, Jaffe JH, Brady JV, Butler CB, Rouse CO, Callaman JM, O'Grady KE, Battjes RJ. 2006. A randomized controlled trial of interim methadone maintenance. *Archives of General Psychiatry*. 63(1):102–109.

Scorzelli JF. 1992. Has Malaysia's antidrug effort been effective. *Journal of Substance Abuse Treatment*. 9(2):171–176.

Secades-Villa R, Fernande-Hermida JR, Arnaez-Montaraz C. 2004. Motivational interviewing and treatment retention among drug user patients: A pilot study. *Substance Use and Misuse*. 39(9):1369–1378.

Sees KL, Delucchi KL, Masson C, Rosen A, Clark HW, Robillard H, Banys P, Hall SM. 2000. Methadone maintenance vs 180-day psychosocially enriched detoxification for treatment of opioid dependence: A randomized controlled trial. *Journal of the American Medical Association*. 283(10):1303–1310.

Sellman JD, Sullivan PF, Dore GM, Adamson SJ, MacEwan I. 2001. A randomized controlled trial of Motivational Enhancement Therapy (MET) for mild to moderate alcohol dependence. *Journal of Studies on Alcohol*. 62:389–396.

Serpellini G, Carrieri MP. 1994. Methadone treatment as a determinant of HIV risk reduction among injecting drug users: A nested case-control study. *AIDS Care*. 6(2):215–220.

Shoptaw S, Reback CJ, Peck JA, Yang X, Rotheram-Fuller E, Larkins S, Veniegas RC, Freese TE, Hucks-Ortiz C. 2005. Behavioral treatment approaches for methamphetamine dependence and HIV-related sexual risk behaviors among urban gay and bisexual men. *Drug and Alcohol Dependence*. 78:125–134.

Shoptaw S, Huber A, Peck J, Yang X, Liu J, Dang J, Roll J, Shapiro B, Rotheram-Fuller E, Ling W. 2006. Randomized, placebo-controlled trial of sertraline and contingency management for the treatment of methamphetamine dependence. *Drug and Alcohol Dependence*. 85(1):12–18.

Shufman EN, Porat S, Witzum E, Gandacu C, Bar-Hamburger R, Ginath Y. 1994. The efficacy of naltrexone in preventing reabuse of heroin after detoxification. *Biological Psychiatry*. 35(12):935–945.

Simpson DD, Joe GW, Rowan-Szal G, Greener J. 1995. Client engagement and change during drug abuse treatment. *Journal of Substance Abuse*. 7:117–134.

Soares BGO, Lima MS, Lima Reisser A, Farrell M. 2003. Dopamine agonists for cocaine dependence. *The Cochrane Database of Systematic Reviews*. (2):CD003352.

Sorenson JL, Copeland AL. 2000. Drug abuse treatment as an HIV prevention strategy: A review. *Drug and Alcohol Dependence*. 59:17–31.

Sorensen JL, London J, Heitzmann C, Gibson DR, Morales E, Dumontet R, Acree M. 1994. Psychoeducational group approach: HIV risk reduction in drug users. *AIDS Education and Prevention*. 6:95–112.

Srisurapanont M, Jarusuraisin N, Kittirattanapaiboon P. 2001. Treatment for amphetamine dependence and abuse. *The Cochrane Database of Systematic Reviews*. (4):CD003022.

Stark K, Muller R, Bienzle U, Guggenmoos-Holzmann I. 1996. Methadone maintenance treatment and HIV risk-taking behaviour among injecting drug users in Berlin. *Journal of Epidemiology and Community Health*. 50:534–537.

Stotts AL, Schmitz JM, Rhoades HM, Grabowski J. 2001. Motivational interviewing with cocaine-dependent patients: A pilot study. *Journal of Consulting and Clinical Psychology*. 69(5):858–862.

Strain EC, Stitzer ML, Liebson IA, Bigelow GE. 1993. Dose-response effects of methadone in the treatment of opioid dependence. *Annals of Internal Medicine*. 119:23–27.

Strain EC, Bigelow GE, Liebson IA, Stitzer ML. 1999. Moderate- vs high-done methadone in the treatment of opioid dependence: A randomized trial. *Journal of the American Medical Association*. 281(11):1000–1005.

Strang J, Marsden J, Cummins M, Farrell M, Finch E, Gossop M, Stewart D, Welch S. 2000. Randomized trial of supervised injectable versus oral methadone maintenance: Report of feasibility and 6-month outcome. *Addiction*. 95(11):1631–1645.

Strang J, McCambridge J, Best D, Beswick T, Bearn J, Rees S, Gossop M. 2003. Loss of tolerance and overdose mortality after inpatient opiate detoxification: Follow up study. *British Medical Journal*. 326:959–960.

Suh JJ, Pettinati HM, Kampman KM, O'Brien CP. 2006. The status of Disulfiram: A half century later. *Journal of Clinical Psychopharmacology*. 26(3):290–302.

Tennant FS, Rawson RA, Cohen AJ, Mann A. 1984. Clinical experience with naltrexone in suburban opioid addicts. *Journal of Clinical Psychiatry*. 45(9 pt 2):42–45.

Termorshuizen F, Krol A, Prins M, Geskus R, van den Brink W, van Ameijden EJ. 2005. Prediction of relapse to frequent heroin use and the role of methadone prescription: An analysis of the Amsterdam Cohort Study among drug users. *Drug and Alcohol Dependence*. 79(2):231–240.

Thiede H, Hagan H, Murrill CS. 2000. Methadone treatment and HIV and hepatitis B and C risk reduction among injectors in the Seattle area. *Journal of Urban Health*. 77(3): 331–345.

Turner BJ, Laine C, Yang CP, Hauck WW. 2003. Effects of long-term, medically supervised, drug-free treatment and methadone maintenance treatment on drug users' emergency department use and hospitalization. *Clinical Infectious Diseases*. 37(Suppl 5):S457.

U.S. FDA (Food and Drug Administration). 2001, March. *Index of Safety-Related Drug Labeling Changes Summaries Approved by the FDA Center for Drug Evaluation and Research (CDER). Medwatch*. [Online]. Available: http://www.fda.gov/medwatch/safety/2001/mar01.htm [accessed June 30, 2006].

van Ameijden EJ, Langendam MW, Coutinho RA. 1999. Dose-effect relationship between overdose mortality and prescribed methadone dosage in low-threshold maintenance programs. *Addictive Behaviors*. 24(4):559–563.

Vanichseni S, Wongsuwan B, Choopanya K, Wongpanich K. 1991. A controlled trial of methadone maintenance in a population of intravenous drug users in Bangkok: Implications for prevention of HIV. *International Journal of Addictions*. 26(12):1313–1320.

Varescon I, Vidal-Trecan G, Nabet N, Boissonnas A. 2002. Buprenorphine abuse: High dose intravenous administration of buprenorphine. *L'Encéphale*. 5(Pt 1):397–402.

Vocci FJ, Elkashef A. 2005. Pharmacotherapy and other treatments for cocaine abuse and dependence. *Current Opinion in Psychiatry*. 18:265–270.

Washton AM, Pottash AC, Gold MS. 1984. Naltrexone in addicted business executives and physicians. *Journal of Clinical Psychiatry*. 45(9 pt 2):39–41.

WHO (World Health Organization), United Nations Office on Drugs and Crime, and Joint United Nations Programme on HIV/AIDS. 2004. *Substitution Maintenance Therapy in the Management of Opioid Dependence and HIV/AIDS Prevention: Position Paper*. Geneva, Switzerland: WHO.

Williams AB, McNelly EA, Williams AE, D'Aquila RT. 1992. Methadone maintenance treatment and HIV type 1 seroconversion among injecting drug users. *AIDS Care*. 4(1): 35–41.

Williamson PA, Foreman KJ, White JM, Anderson G. 1997. Methadone-related overdose deaths in South Australia 1984–1994. *Medical Journal of Australia*. 166: 302–305.

Yancovitz SR, Des Jarlais DC, Peyser NP, Drew E, Friedmann P, Trigg HL, Robinson JW. 1991. A randomized trial of an interim methadone maintenance clinic. *American Journal of Public Health*. 81(9):1185–1191.

3

Sterile Needle and Syringe Access, and Outreach and Education

For those who are unable to stop using or injecting drugs, sterile needle and syringe access aims to reduce HIV transmission by increasing access to sterile injecting equipment, removing contaminated needles from circulation, and preventing needles and syringes from being discarded in the community, where others might reuse them or suffer needle sticks. Access can be ensured through needle and syringe exchange, pharmacy and prescription-based sales, vending machines, supervised injecting facilities, and disinfection programs. Many sterile needle and syringe access programs also encourage the cessation of drug abuse through referrals to drug treatment, and the reduction of sex-related risk through the provision of condoms. All these interventions can be combined with outreach and education.

This chapter starts with a discussion of needle and syringe exchange (NSE).[1] In many regions of the world where it has been implemented and evaluated, needle and syringe exchange is usually part of a multi-component HIV prevention effort. To properly reflect this, the Committee refers to such programs as multi-component HIV prevention programs

[1]Needle and syringe exchange refers broadly to supplying clean needles and syringes to IDUs and collecting used injecting equipment. While some programs require exchange of used needles for clean ones, need-based programs allow unlimited distribution of needles and syringes.

that include needle and syringe exchange. These are defined as interventions that combine needle and syringe exchange with any one or more of the following services: outreach, health education in risk reduction, condom distribution, bleach distribution coupled with education on needle disinfection, and referrals to substance abuse treatment and other health and social services. In this report, the term multi-component HIV prevention programs does not include drug dependence treatment and other medical or social services (discussed in Chapter 2), but does include referrals to these services. While this separation may seem somewhat artificial, the Committee felt it was necessary to accurately describe the evidence related to needle and syringe exchange.

The following two sections then examine alternatives to NSE for providing access to clean injecting equipment. One of these two sections focuses on pharmacy and prescription sales, vending machines, and supervised injecting facilities, while the other section focuses on disinfection distribution and education programs.

The chapter then evaluates empirical evidence on the effectiveness of outreach and education in preventing HIV transmission among IDUs. Outreach and education are sometimes part of multi-component HIV prevention programs, as they are often used to direct drug users to services such as needle and syringe exchange. They can also stand alone as a means of educating IDUs on HIV prevention, and can also be used to refer drug users to drug treatment and other health and social services. The final section of the chapter discusses specific areas in need of further research in high-risk countries.

NEEDLE AND SYRINGE EXCHANGE

To evaluate the effectiveness of NSE, the Committee reviewed studies identified by a literature review (see Appendix B). As discussed in Chapter 2, the Committee then used a structured qualitative method based on an approach developed by the GRADE Working Group to evaluate the strength of the evidence (GRADE Working Group, 2004) (see Chapter 2 for further detail).

The majority of evidence on the effectiveness of NSEs comes from observational studies, including numerous prospective cohort studies, supplemented by results from ecological and cross-sectional studies. (Appendix D provides a summary of these studies, grouped by study design.) The Committee did not identify any randomized controlled trials of NSE. This is not completely unexpected for such a public health intervention, particularly one with such immediacy and assumed efficacy and face validity. The Committee identified three case-control studies. Such studies enroll participants based on the presence or absence of a disease, and then com-

pare the characteristics of a previous exposure to NSE. The Committee identified 26 prospective cohort studies, which enroll participants based on their risk characteristics, and follow them to compare related outcomes. The committee felt that 14 of these studies were especially strong in terms of study design and relevance (and noted those studies with an asterisk in a table in Appendix D). Case-control and prospective cohort studies were ranked as having the strongest available study design.

The Committee also identified six ecological studies, which examine populations rather than individuals and cannot establish causal links. Finally, the Committee identified many cross-sectional and serial cross-sectional studies. Cross-sectional studies describe the associations between a disease and risk factors in a population at a specific point in time. The Committee considered such studies as having the weakest design because causal inferences cannot be drawn from them. Serial cross-sectional studies examine groups of people at multiple time points, and offer stronger evidence of shifts in associations over time. As opposed to prospective cohort studies which examine individual-level changes in risk behavior, well-designed serial cross-sectional studies can indicate patterns of behavior change at the community level. As supporting evidence, the Committee included six cross-sectional and four serial cross-sectional studies in Appendix D, based on their strong study design and relevance to the Committee's statement of task.

The Committee used caution in interpreting the results of studies reviewed in this chapter because of their generally weak designs and serious limitations. One limitation is that the studies identified do not randomly assign subjects to treatment and control groups—rather, participants deliberately choose whether to use NSEs and other services. This creates an unavoidable risk of selection bias, and means that differences in rates of risk behaviors and HIV infection may not be due to use of the service itself. Another limitation is that the study designs generally do not allow separate examination of program elements, so the independent contribution of improving access to sterile needles and syringes cannot be assessed. For example, NSE is often one component of a multi-component HIV prevention program, making it difficult to isolate the exact effects of NSE alone.

Another concern is that studies of drug abuse, like most behavioral research, depend heavily on self-reported data on drug use, risk behavior, and precautions taken to reduce risk. Studies evaluating the effectiveness of NSEs are no exception. Self-reported data can introduce bias, as drug abuse is illegal in most settings, and drug users may underestimate risk behavior and overestimate protective behavior. Still, the self-reports of drug users on the incidence of drug abuse and drug-related risks have generally been shown to be valid (Darke, 1998) and remain the major type of outcome measures used in studies of NSE.

Studies comparing audio computer-assisted self-interviews with interviewer-administered surveys show that IDUs tend to under-report risk behavior such as needle sharing (Metzger et al., 2000; Des Jarlais et al., 1999) and over-report protective behaviors such as condom use and syringe disinfection (Macalino, 2002) in face-to-face interviews. However, Safaeian et al. (2002) compared self-reports to NSE records and found that the majority of self-reports of NSE attendance in Baltimore were valid. This study also found that persons who over-reported NSE attendance were more likely to have injected frequently (adjusted odds ratio [AOR]=1.29; 95% confidence interval [CI]: 1.04–1.61), denied needle sharing (AOR=0.69; 95% CI: 0.52–0.89), and seroconverted to HIV (AOR=1.83; 95% CI: 1.11–.01). In the Baltimore study, model predictors of HIV infection based on self-reports compared with actual program data underestimated the protective effect of NSE participation by 18 percent (Safaeian et al., 2002).

Evaluations of NSE often include a range of outcome measures (see Box 3.1). Desirable outcomes may include a reduction in high-risk behavior, more referrals to drug treatment, and declines in rates of HIV infection. Negative outcomes may include more frequent injection among participants, new initiates to injecting drug use, greater drug use in the community, and more needles discarded in public places. In the following sections,

BOX 3-1 Potential Outcomes from Needle and Syringe Exchange

Drug-related risk behavior
- Frequency of drug use
- Frequency of injection
- Frequency of equipment sharing
- Use of disinfectant
- Number of injecting partners

Sex-related risk behavior
- Number of sexual partners
- Frequency of unprotected sex
- Sale of sex for drugs or money

Unintended consequences
- Recruitment of new IDUs
- Increase in unsafe disposal of needles
- Increase in prevalence or frequency of drug use

Links to health and social services
- Referral to services
- Extent of use of services
- Referral to drug treatment

Incidence/prevalence
- HIV
- Hepatitis C
- Hepatitis B

the Committee presents evidence categorized by outcome measure, including the impact of NSEs on drug-related and sex-related risk behavior, the impact of NSEs on HIV incidence and prevalence, any unintended consequences, and the impact of NSEs on links to health and social services.

Drug-Related Risk Behavior

The Committee did not identify any case-control studies that examined the impact of multi-component programs that include needle and syringe exchange on drug-related risk behavior. As noted, the Committee considered prospective cohort studies the strongest study design along with case-control studies. Of 26 prospective cohort studies identified, 18 examined the impact of these programs on drug-related risks. Thirteen found that participation in multi-component programs that include needle and syringe exchange reduced self-reported needle sharing. (Sharing is defined as lending or borrowing used needles or syringes.) Four studies found no increase in injection frequency among NSE participants, and one of these found a decrease (see Appendix D and Table 3.1). The sections below discuss studies selected by the Committee for their strong study design and relevance.

Sharing drug preparation equipment such as cookers used to melt drugs, cotton used to filter out particles when drawing the drug into the syringe, and water used to rinse syringes, has been associated with hepatitis C (HCV) infection (Diaz et al., 2001; Hagan et al., 1999, 2001; Hahn et al., 2002; Thorpe et al., 2002). Few studies have examined whether NSEs reduce the sharing of other injection equipment such as cookers, cotton, or water—possibly because NSEs do not always provide such equipment. One prospective cohort study by Ouellet et al. (2004) shows that when NSEs do provide such drug paraphernalia, sharing declines. A cross-sectional study in Providence, Rhode Island, where an NSE provides alcohol swabs and cookers, supports this finding (Longshore et al., 2001). Two prospective cohort studies found no association between NSE use and the sharing of other injecting equipment (Hagan et al., 2000; Huo et al., 2005).

In 2004 in Chicago, Ouellet et al. compared NSE users (n=558)—defined as those who obtained at least half their needles from an NSE—to non-users (n=175). Non-users were recruited from a neighborhood that did not have an NSE. Using multivariate analysis, the researchers found that regular NSE users were less likely to share needles (AOR=0.30; 95% CI: 0.19-0.46), lend used needles (AOR=0.47; 95% CI: 0.31–0.71), or use a needle for more than one injection (AOR=0.15; 95% CI: 0.08–0.27).

Similarly, Bluthenthal and colleagues (2000) interviewed 340 street-recruited IDUs semi-annually to determine whether NSE use was associated with a decrease in syringe sharing. IDUs participating in the study also received HIV testing and counseling at the time of interview. The study

found that 60 percent reported cessation of syringe sharing. Compared with non-NSE users, IDUs who began using an NSE were more likely to stop sharing syringes (AOR=2.68; 95% CI: 1.35–5.33), as were those who continued using the NSE (AOR=1.98; 95% CI: 1.05–3.75).

Schoenbaum and colleagues (1996) studied the injection behavior of NSE users and non-users in the Bronx, New York City. The study found that male gender, HIV-seropositive status, and younger age were independently associated with NSE attendance, and that NSE users shared needles less often than non-users ($p<0.05$).

A study by Gibson et al. (2002) examined whether NSE use is protective against high-risk behavior such as more frequent injection and syringe borrowing. The study sample included 338 untreated opiate-addicted IDUs, 77 percent of whom were included in follow-up (n=212). The study found that NSE users did not differ from non-users in injection frequency, but were less likely to report borrowing a used syringe. In univariate analysis, NSE use was protective against HIV risk (OR=0.45; 95% CI: 0.21–0.92). Multivariate analyses were used to correct for potential differences between IDUs who use NSE versus those who choose not to. These analyses found that NSE use had a more than six-fold protective effect against HIV risk behavior among IDUs using NSE as their sole source of syringes.

In Baltimore, Vlahov et al. (1997) examined the drug-related behavior of 221 NSE participants at entry into the NSE, 2 weeks after entry, and 6 months after entry. At 6-month follow-up, reductions were reported in using a previously used syringe, lending syringes, backloading (drawing drug into a syringe and then transferring a portion into a second syringe by removing the plunger), and sharing cookers and cotton.

A few studies have found that NSEs have no effect on drug-related risk behavior. For example, in a prospective cohort study in Amsterdam, Hartgers et al. (1992) found that NSE users did not borrow needles and syringes more or less often than non-NSE users. A cross-sectional study by Hagan et al. (1993) interviewed NSE users and asked about injection behavior during the month before first use of the NSE and the most recent month since starting to use the NSE. The study found no change in self-reported frequency of injection, but did find a decline in self-reported frequency of unsafe injection.

Based on this evidence, the Committee concludes:

Conclusion 3-1: Nearly all programs included in our literature search combine needle and syringe exchange with other components such as outreach, risk reduction education, condom distribution, bleach distribution and education on needle disinfection, and referrals to substance abuse treatment and other health and social services.

TABLE 3-1 Studies with Drug-Related Risk Outcomes

Study	Result
Bluthenthal et al., 2000, California (prospective cohort)+	NSE users decreased syringe sharing.
Bruneau et al., 2004, Montreal (prospective cohort)+	NSE and pharmacy users less likely to stop injecting.
Cox et al., 2000, Ireland (prospective cohort)	NSE users decreased needle and syringe sharing and frequency of drug use.
Des Jarlais et al., 2000, New York City (ecological)	Injection risk behaviors declined significantly in presence of NSE.
Gibson et al., 2002, California (prospective cohort)+	NSE users decreased syringe sharing; no change in injecting frequency.
Hagan et al., 2000, Seattle, Washington (prospective cohort)+	NSE users less likely to inject with a used syringe; no association with sharing of other injection equipment.
Hagan et al., 1993, Tacoma, Washington (cross-sectional)	NSE users report no change in frequency of injection; the frequency of unsafe injection declined.
Hammett et al., 2006, Vietnam and China (serial cross sectional)	Drug-related risk behavior declined in frequency.
Hart et al., 1989, London (prospective cohort)	NSE users decreased syringe sharing; no increase in frequency of injection.
Hartgers et al., 1992, Amsterdam (prospective cohort)	No difference in sharing between NSE users and non-users.
Huo et al., 2005, Chicago (prospective cohort +	NSE users less likely to share syringes; no association with sharing of other injection equipment.
Keene et al., 1993, Wales (cross-sectional)+	NSE users less likely to share syringes.
Klee et al., 1991, UK (cross-sectional)	NSE users more likely to lend syringes.
Longshore et al., 2001, Providence, Rhode Island (cross-sectional)	NSE users less likely to report syringe sharing; more likely to report cleaning their skin; less likely to report sharing cookers.
Marmor et al., 2000, New York City (prospective cohort)	NSE users decreased rates of drug injecting.
Monterroso et al., 2000, multiple U.S. cities (prospective cohort)	NSE users less likely to share needles and syringes.
Ouellet et al., 2004, Chicago (prospective cohort)+	NSE users decreased sharing of needles, syringes, and other equipment.
Schoenbaum et al., 1996, New York City (prospective cohort)+	NSE users shared less than non-NSE users.
Van Ameijden and Coutinho, 1998, Amsterdam (prospective cohort)	NSE users showed large initial reduction in sharing needles and frequency of injection.
Van Ameijden et al., 1994, Amsterdam (serial cross sectional)	NSE users are less likely to reuse needles/ syringes.

continued

TABLE 3-1 Continued

Study	Result
Van den Hoek et al., 1989, Amsterdam (prospective cohort)	NSE users decreased needle and syringe sharing; no increase in frequency of drug use.
Vazirian et al., 2005, Iran (cross-sectional)	NSE users decreased needle/syringe sharing.
Vertefeuille et al. 2000, Baltimore (prospective cohort)	NSE users decreased syringe sharing; increased participation in drug treatment.
Vlahov et al., 1997, Baltimore (prospective cohort)	NSE users decreased syringe sharing.
Watters et al., 1994, San Francisco (serial cross-sectional)	NSE users reported decrease in frequency of injection; less likely to share needles/syringes.
Wood et al., 2002, Vancouver (prospective cohort)+	NSE users less likely to share needles and syringes.
Wood et al., 2003, Vancouver (prospective cohort)	NSE users more likely to frequently inject cocaine; more likely to safely dispose of syringes.

+ Indicates that the study compared NSE users with non-users.

Conclusion 3-2: Moderate evidence from a large number of studies and review papers—most from developed countries—shows that participation in multi-component HIV prevention programs that include needle and syringe exchange is associated with a reduction in drug-related HIV risk behavior. Such behavior includes self-reported sharing of needles and syringes, safer injecting and disposal practices, and frequency of injection.

Sex-Related Risk Behavior

Few studies have evaluated the effect of NSEs on sex-related HIV risk behavior (see Table 3-2). This is not surprising, because reduction in sexual risk (often evaluated by reports of condom use) is often not a primary goal of NSEs. However, two early prospective cohort studies associated use of an NSE with a decline in the number of sexual partners (Donoghoe et al., 1989; Hart et al., 1989). Donoghoe and colleagues measured the sexual behavior of 142 NSE clients in England and Scotland at baseline and 2 to 4 months later. Seventy-seven percent of clients reported having one or more sexual partner in the 3 months prior to the first interview. Forty-six percent of these sexually active clients had non-IDU partners. At follow-up, the number of NSE clients having no sexual partners increased from 23 to 31

TABLE 3-2 Studies with Sex-Related Risk Outcomes

Study	Result
Donoghoe et al., 1989, UK (prospective cohort)	Number of NSE participants having no sexual partners increased; number having multiple sexual partners decreased.
Hart et al., 1989, London (prospective cohort)	Significant correlation between multiple sexual partners and condom use; and a reduction in the proportion of clients with multiple partners.
Cox et al., 2000, Ireland (prospective cohort)	NSE users reported no significant change in levels of condom use.

percent, and the number having multiple partners decreased slightly from 26 to 21 percent.

Hart et al. (1989) monitored an NSE in London and followed 121 NSE clients from November 1987 to October 1988. Clients were interviewed 1 month after entry into the NSE and again three months later. The study found a highly significant correlation between multiple sexual partners and condom use, and a reduction in the proportion of NSE clients with multiple partners.

Based on this evidence, the Committee concludes:

Conclusion 3-3: Needle and syringe exchange is not primarily designed to address sex-related risk behavior. In two early prospective cohort studies, NSE participants reported decreases in sex-related risk behavior. However, this issue has not been well studied, and the existing modest evidence is insufficient to determine the effectiveness of needle and syringe exchange in reducing sex-related risk.

Effects of NSE on HIV Incidence/Prevalence

Few site-specific studies have explored the relationship between NSE participation and HIV incidence, although several ecological studies have found positive associations between the introduction or presence of NSEs and reduced HIV prevalence and incidence (see Table 3-3). As mentioned, whether NSE alone is responsible for the impacts is unclear, given myriad design and methodological issues noted in the majority of studies.

Two prospective cohort studies from Montreal and Vancouver in the 1990s associated NSE participation with higher risk of HIV seroconversion (Strathdee et al., 1997; Bruneau et al., 1997). In Montreal, Bruneau et al.

TABLE 3-3 Studies with HIV Incidence or Prevalence Outcomes

Study	Result
Bruneau et al., 1997, Montreal (prospective cohort)	Increased HIV seroconversion among NSE users.
Des Jarlais et al., 2005a, New York City (ecological)	From 1990–2001, HIV prevalence declined.
Des Jarlais et al., 2005b, New York City (serial cross-sectional)	Strong negative relationship between the number of syringes exchanged and estimated HIV incidence.
Hammett et al., 2006, Vietnam and China (serial cross-ectional)	HIV prevalence among IDUs declined in Vietnam and remained stable in China.
Hurley et al., 1997, worldwide (ecological)	Increased HIV prevalence in cities without NSE.
MacDonald et al., 2003, worldwide (ecological)	Increased HIV prevalence in cities without NSE.
Mansson et al., 2000, Sweden (prospective cohort)	No new HIV cases during a median of 31 months among NSE participants.
Patrick et al., 1997, Vancouver (case control)	No association with frequency of NSE use and HIV seroconversion.
Schechter et al., 1999, Vancouver (prospective cohort)	Cumulative HIV incidence was significantly elevated in frequent NSE attenders.
Strathdee et al., 1997, Vancouver (prospective cohort)	Increased HIV and HCV prevalence in the presence of NSE.
Van Ameijden et al., 1992, Amsterdam (case control)	No association between NSE participation and HIV seroconversion.

(1997) used three risk-assessment approaches to examine the association between NSE use and HIV infection. All three analytical approaches associated NSE attendance with a substantial and consistently higher risk of HIV infection. For example, in the cohort approach, in which there were 89 incident cases of HIV infection, the researchers found a 33 percent cumulative probability of HIV seroconversion for NSE users, compared with a 13 percent probability for non-users. In the nested case-control study, consistent NSE use was associated with HIV seroconversion during follow-up (OR=10.5; 95% CI: 2.7–41.0). The analyses employed methodologies to control for a range of confounders, including drug of choice and frequency of injecting drug use in the previous month. These findings persisted after controlling for confounders.

The authors and commentators on this research pointed out that the Montreal NSE appeared to have attracted high-risk cocaine injectors, who injected much more often than heroin users. Also, as shown by the seroprevalence data at baseline, Montreal NSE users had high baseline rates of HIV and hepatitis B infection (Bruneau et al., 1997). The NSE also originally strictly limited the number of needles and syringes users could

receive during any one visit. The authors further noted that the ready availability of clean injecting equipment through pharmacies might have meant that the NSE attracted marginalized, high-risk individuals (Bruneau et al., 1997).

These early research results prompted the Montreal NSE to remove limits on the number of needles and syringes users could obtain, to provide access to other injection equipment, and to expand the number of distribution points to 25 (Personal communication, Carole Morissette and Pascale Leclerc, Health Protection Sector, Public Health Department, Agence de Santé et Des Services Sociaux de Montréal, June 6, 2006). In addition to syringes, NSEs began to provide alcohol swabs, individual disposal containers, sterile water vials, and "stericups" (kits containing a filter, cooker, and post-injection swab). Of 429 pharmacies in Montreal, injection equipment is available at roughly 40 percent, and some (n=70) sell kits containing four syringes, condoms, alcohol swabs, sterile water vials, stericups, and education material for $1.

Following these changes, HIV incidence among participants in the Montreal SurvUDI study dropped from 6.1 per 100 person-years in 1995 to 4.7 per 100 person-years in 2004. The SurvUDI study is a surveillance network that began in 1995 and targets hard-to-reach, mostly out-of-treatment IDUs in Eastern Central Canada (Hankins et al., 2002). HCV incidence—reported retrospectively among Montreal SurvUDI participants between 1997 and 2003—remains high, at about 26 per 100 person-years. (Personal communication, Carole Morissette and Pascale Leclerc, Health Protection Sector, Public Health Department, Agence de santé et des services sociaux de Montréal, June 6, 2006). The SurvUDI network also provides data on trends in syringe sharing in Montreal, including the proportion of participants injecting with a syringe used by someone else (at first study participation). That proportion fell from 45 percent in 1995 to 28 percent in 2004.

In Vancouver, Strathdee et al. (1997) also found that frequent NSE attendance was an independent predictor of HIV seroconversion. After adjusting for confounders, the authors found that the adjusted odds ratio for HIV infection status among NSE users compared with non-NSE users was 1.68. The authors noted that cocaine was the drug of choice among 72 percent of HIV-seropositive IDUs, and that cocaine puts IDUs at elevated risk because it is associated with more frequent injection (Anthony et al., 1991; Chaisson et al., 1989). A follow-up study by Schechter et al. (1999) in the same setting found no relationship between NSE use and HIV incidence, and a case-control study found borrowing of syringes to be the most significant behavior associated with seroconversion among IDUs (Patrick et al., 1997). After multivariate analysis controlling for confounders, the au-

thors found no association between frequency of NSE use and seroconversion.

As in Montreal, the Vancouver NSE originally operated with strict limits on the number of needles and syringes that users could exchange at any one time, and the program operated in only one location. The Vancouver program also made dramatic changes in response to early results. Specifically, the NSE switched from a limited exchange approach to a need-based approach—allowing unlimited distribution of needles/syringes—and greatly increased the number of access points. The program also began offering a variety of distribution methods, including fixed, mobile, and home delivery. HIV incidence among IDUs has since fallen by 30 percent (Personal communication, Chris Buchner, Vancouver Coastal Health Authority, May 5, 2006).

Several studies in Amsterdam found no significant relationship in either direction between NSE participation and HIV incidence (van Ameijden et al., 1992; Coutinho, 2005). Several other papers by these authors (van Ameijden and Coutinho, 1998, 2001) found initial reductions in risk behavior after NSE and other interventions began, but no further reductions over time. These studies also found that NSE was not associated with an increase in injecting drug use, and attributed declines in injecting to cultural and ecological factors. Krol (2006) reached the same conclusion.

Several ecological studies from the developed world found that early, comprehensive programs of outreach, prevention, education, and access to sterile injecting equipment may prevent the expansion of IDU-driven epidemics. Ecological studies, as well as serial cross-sectional studies, reflect community-level patterns of prevalence and risk behaviors rather than patterns or changes at the individual level. For example, Des Jarlais et al. (1995) examined five cities (Glasgow, Scotland; Lund, Sweden; Sydney, Australia; Tacoma, U.S.; and Toronto, Canada) where HIV was introduced into the IDU population but infection rates remained below 5 percent for at least 5 years. The authors found that all five cities had pursued early prevention activities, such as offering sterile injection equipment and community-based outreach. Such interventions may also help reduce HIV prevalence and incidence among IDUs in more mature HIV epidemics, such as in New York City (Des Jarlais et al., 2005a).

In a study of 81 cities, Hurley and colleagues (1997) found that annual HIV seroprevalence between 1988 and 1993 rose by 5.9 percent in 52 cities without NSEs, and fell by 5.8 percent in 29 cities with NSEs. In a similar analysis of 99 cities, MacDonald and colleagues (2003) found that annual HIV prevalence fell by 18.6 percent in cities that introduced NSEs, and rose by 8.1 percent in cities without NSEs. Critics objected that this study did not account for the stage of the epidemic in these cities, and that the researchers used different protocols to collect data on seroprevalence in

different populations (Käll, 2005). To address the possibility that the effect of NSEs can vary with the stage of epidemic, both Hurley et al. and MacDonald et al. analyzed cities where the initial measured seroprevalence among IDUs was less than 10 percent. In the Hurley et al. study, the authors did not find a significant association between NSE presence and the trajectory of the epidemic. However, MacDonald and colleagues did find a significant relationship: the mean annual weighted increase in HIV prevalence was 32.1 percent in cities that did not introduce NSEs, compared with a mean annual decrease of 7.8 percent in cities with NSEs (p=0.03).

Multiple studies show that NSEs do not reduce transmission of HCV, which has been attributed to the apparent failure of NSEs to provide enough ancillary injecting equipment such as sterile cotton, water, and alcohol wipes. While NSEs do reduce the frequency of reported needle and syringe sharing, they do not appear to reduce the sharing of other injecting equipment, such as cookers, cotton, rinse water, and drug solution (Hagan and Thiede, 2000; Sarkar et al., 2003; Taylor et al., 2000; Mansson et al., 2000). In contrast, a case-control study by Hagan et al. (1995) in Seattle found that NSE attendance was associated with a six-fold decrease in acquisition of hepatitis B virus (HBV), and a seven-fold decline in HCV acquisition. Given the high prevalence of HCV among IDUs, this represents an important area for future research.

Based on this evidence, the Committee concludes:

Conclusion 3-4: Four ecological studies have associated implementation or expansion of HIV prevention programs that include needle and syringe exchange with reduced prevalence of HIV in cities over time and after considering the local prevalence of HIV at the time of program implementation or expansion—although a causal link cannot be made based on these studies. The evidence of the effectiveness of NSE in reducing HIV prevalence is considered modest, based on the weakness of these study designs.

Conclusion 3-5: Moderate evidence indicates that multicomponent HIV prevention programs that include needle and syringe exchange reduce intermediate HIV risk behavior. However, evidence regarding the effect of needle and syringe exchange on HIV incidence is limited and inconclusive.

Conclusion 3-6: Five studies provide moderate evidence that HIV prevention programs that include needle and syringe exchange have significantly less impact on transmission and acquisition of hepatitis C virus than on HIV, although one case-control study shows a dramatic decrease in HCV and HBV acquisition.

Mathematical Models

A previous National Research Council and Institute of Medicine (IOM) report (NRC and IOM, 1995) and a University of California review (Lurie et al., 1993) reviewed mathematical models and their conclusions regarding the impact of NSE on HIV incidence. Thus this section will examine such models only briefly, and the evidence presented is considered supplementary to the empirical studies described above.

Mathematical models used by Kaplan and colleagues (Kaplan and Heimer, 1992; Kaplan and O'Keefe, 1993) used a set of two dynamic equations and their associated steady states to link the size of NSE programs to HIV incidence in injecting equipment and IDUs (Kaplan and O'Keefe, 1993). A syringe tracking system developed for this purpose allowed the researchers to assess infection rates in injecting equipment directly from an existing NSE in New Haven, Connecticut. The researchers used those rates to infer the impact of New Haven's needle and syringe exchange on HIV incidence among IDUs. A key finding was that the NSE reduced steady state prevalence in injecting needles by one-third. From this, the researchers deduced that HIV incidence also fell by one-third in steady state. A separate modeling exercise showed that annual HIV incidence fell by 1–3 per 100 participant-years.

More recently, a variant of this mathematical framework has been used to assess the impact of extending coverage of needle distribution programs on HIV transmission among injecting drug user populations of Belarus and the United Kingdom when injectors share needles in the confines of small sub-groups of the population (Vickerman et al., 2006). Its main finding, based on simulations, is that the biggest reductions in steady-state HIV prevalence usually occur only after certain threshold levels of service coverage have been achieved.

Questions have been raised about the underlying technical assumptions of mathematical models in general and specifically the New Haven studies. One concern is whether the law of conservation of needles—a key element of the Kaplan model—is valid in practice. This law requires that the number of new needles handed out and the number handed in be roughly the same. This was the case with the New Haven NSE, and the weight of evidence for other NSE programs supports this assumption (Guydish et al., 1991; Ksobiech, 2004).

A second issue is whether the composition of program participants changed over time—for instance, whether persons more likely to be HIV-seropositive dropped out of the program and were replaced by persons less likely to be HIV-seropositive. Under this scenario, the model would tend to overestimate the effectiveness of NSE. Kaplan et al. (1994) argue that little evidence suggests that such a shift occurred in the New Haven NSE.

A third area of concern is the model's relative lack of attention to behavioral aspects of HIV transmission. For instance, Bloom et al. (2006) argue that needles turned in to the needle exchange program are likely to be older and to have been used more frequently—not a random selection of circulating needles. Thus infection rates among these old needles are likely to be "terminal" rather than "average." These two rates can sometimes move in opposite directions, so the data for New Haven may not offer ready insight into the impact of NSE on HIV incidence among humans. Additionally, in the case of the model used for the Belarus and United Kingdom study (Vickerman et al., 2006), we do not know how the size and composition of injecting drug user sharing groups respond to needle distribution programs and hence their efficacy in reducing HIV transmission.

After evaluating these concerns, the IOM review (NRC and IOM, 1995) concluded: "The model-based evaluation of the New Haven needle exchange program provides important insights into the dynamics of such programs and useful preliminary estimates of their efficacy. We cannot attach the same level of confidence to these model-based estimates as we could to evaluation programs that included a suitable control group in which individuals were tested (directly) for HIV infection" (p. 231).

While there are questions about specific numerical estimates of the efficacy of needle exchange programs derived from mathematical models of HIV transmission among IDU, such models do have the advantage of illustrating the relationships among the major parameters such as the probability of transmission, the size of needle sharing groups and the frequency of shared needle use that influence the transmission of HIV among IDU. Moreover, models can highlight some common areas of concern such as how the relatively high probability of transmission of HCV from a single unsafe injection means that even if needle exchanges achieved high coverage rates, they would be much less efficacious in preventing HCV than HIV.

Unintended Consequences of Needle and Syringe Exchange

This section reviews evidence regarding the effect of NSE on the frequency of drug use, the recruitment of new injecting drug users, unsafe disposal of needles, and trends in crime. The Committee did not identify any studies that focus on these outcomes as their main objective, but some studies report them as secondary outcomes.

Of the prospective cohort studies (see Appendix D), five found no increase in frequency of injecting among NSE attenders (Hart et al., 1989; van Den Hoek et al., 1989; Cox et al., 2000; Gibson et al., 2002; Marmor et al., 2000). Hart et al. (1989) found that the frequency of injecting did not increase among NSE clients in London, and that the incidence of drug use-related abscesses fell among this group. van Den Hoek et al. (1989) found

no increase in the proportion of participants injecting drugs or the frequency of drug use among 263 IDUs in Amsterdam. A serial cross-sectional study in San Francisco found that NSE users reported a drop in injections from 1.9 to 0.7 per day (Watters et al., 1994).

Other studies suggest that programs that include NSE do not increase the number of new IDUs. During a 5.5-year study period, Watters et al. (1994) found that the proportion of persons who reported first injecting drugs in the previous year decreased from 3 to 1 percent. In Tacoma, Washington, Hagan et al. (1993) found no increase in drug use. The study measured initiation into drug use by collecting injection histories of NSE users. Only 1 of 204 users began using drugs after the NSE opened, and only 13 users had started injecting in the previous 2 years. In Vancouver, when NSE users were asked where they had met their new sharing partners, only 1 of 498 cited the NSE (Schechter et al., 1999).

Studies have not linked NSEs to a higher number of discarded used needles (Oliver et al., 1992; Broadhead et al., 1999; Doherty et al., 2000). A prospective study in Ireland by Cox et al. (2000) found that at 6-month follow-up, the proportion of NSE users discarding needles in the street, alley, sewer, or gutter declined from 28.2 percent to 15.6 percent ($p< 0.001$), and the proportion discarding needles in the garbage or a dumpster fell from 42.4 percent to 29.1 percent ($p<0.001$). Similarly, a prospective study in Vancouver by Wood et al. (2003) found that NSE use was independently associated with safer syringe disposal (AOR=2.69; 95% CI: 1.38–5.21).

A study in Baltimore examined whether the introduction of a needle and syringe exchange was associated with increased crime rates (Marx et al., 2000). Using arrest records, the study compared trends in arrests in NSE areas and non-NSE areas of the city before and after introduction of the NSE. Arrest trends were modeled and NSE areas were compared to non-NSE areas. No significant differences were found (Marx et al., 2000). A cross-sectional study in an inner-city neighborhood of New York City assessed the association between proximity to an NSE and violence (Galea et al., 2001). Results showed no significant association between distance from the nearest NSE and reporting a fight (OR=1.05; p=0.89); robbery in the neighborhood in the previous 6 months (OR=1.13; p=0.71); having ever experienced violence (OR=0.72; p=0.52); or having ever been robbed by drug users (OR=1.05; p=0.91) (Galea et al., 2001).

Based on this evidence, the Committee concludes:

Conclusion 3-7: Few studies have specifically evaluated whether HIV prevention programs that include needle and syringe exchange lead to unintended consequences, such as increases in new drug users, more frequent injection among established users, ex-

panded networks of high-risk users, more discarded needles in the community, and changes in crime trends. Modest evidence shows that NSE does not increase the number of discarded needles in the community, and that injection frequency does not increase among NSE participants. Weak evidence and limited data suggest that programs that include NSEs do not lead to new users, expanded drug networks, or increases in crime.

Links to Health and Social Services

NSEs can serve as important links to health and social services for drug users who otherwise might not have access to treatment and care. Examples of such services include referrals to drug treatment, voluntary HIV counseling and testing, and medical care such as vaccinations and diagnosis of infections.

To assess the role of NSEs as a bridge to treatment, Strathdee et al. (1999) conducted a prospective cohort study in Baltimore. The study found that NSE attendance and health care use were each independently associated with entry into detoxification. HIV-seropositive NSE attenders were more than three times as likely to enter a detoxification program in the first year after the NSE began, but this result diminished over time. One explanation is that IDUs seeking treatment visited the NSE in large numbers when it first opened. A study at a New Haven NSE found that known syringe exchangers accounted for only 27 percent of requests for drug treatment (Heimer, 1998). Among the requesters, there was a strong association between heroin use and use of the NSE, and between alcohol use and non-users. This reveals that many people seeking drug treatment are not NSE clients, and that a treatment referral program could reach a larger target audience.

IDUs are likely to use services offered through an NSE beyond referrals for drug treatment. Porter et al. (2002) conducted a cross-sectional study at a needle and syringe exchange in Philadelphia offering four types of services: HIV voluntary counseling and testing, medical care, drug treatment referrals, and referrals to other services. The sample (n=43) included needle and syringe exchange users and non-users. Thirty-nine percent of the sample used at least one service besides needle exchange, with most of these participants using services that did not require outside follow-up. Twenty-eight percent had heard of at least one service beyond needle and syringe exchange, but had not used the additional service. Reasons for not using available services included access to these services through other means, and unwillingness to spend time waiting for them. The remaining study participants were either not aware that additional services existed or were aware that other services were available but had no knowledge of the

specifics types. All the respondents who used the needle exchange fell into the first two categories, while non-users fell into the latter two.

Examining the characteristics of NSE participants associated with health care and drug treatment (n=269) in Baltimore, Riley et al. (2002) found that 58 percent reported using primary health care in the previous 3 years. Being age 40 years or older, having health insurance, and exchanging more than seven syringes per visit were positively associated with use of primary health care.

Some studies have illustrated the range of unique health services provided with NSEs. For example, a study by Grau et al. (2002) described a wound and abscess clinic incorporated into an NSE in Oakland, California. In New York City, an NSE administered influenza and pneumococcal vaccines to IDUs (Stancliff et al., 2000); while in Baltimore an NSE provided tuberculosis services (Riley et al., 2002).

Pollack et al. (2002) examined whether a mobile NSE-based health care delivery system reduced the use of hospital emergency rooms by out-of-treatment IDUs in New Haven. Of 373 IDUs, 117 were NSE clients and 256 were not. After the system was implemented, use of the emergency room fell among clients and rose among non-clients.

Based on this evidence, the Committee concludes:

Conclusion 3-8: Few empirical studies have evaluated whether HIV prevention programs that include needle and syringe exchange effectively link IDUs to ancillary health and social services. The few studies examining this issue show moderate uptake of these services among NSE attendees. However, none of the studies had comparison or control groups, so the overall use of such services among drug users who do not use NSE is unknown.

Summary Conclusion and Finding on Multi-Component HIV Prevention Programs that Include NSE

Summary Conclusion: Moderate evidence from developed countries points to a beneficial effect of multi-component HIV prevention programs that include needle and syringe exchange on injection-related HIV risk behavior, such as self-reported needle sharing and frequency of injection. Modest evidence also points to decreasing trends in HIV prevalence in selected cities studied over time. Although many of the studies have design limitations, the consistency of these results across a large number of studies supports these conclusions.

Finding 3-1: The Committee finds that almost all published studies of multi-component HIV prevention programs that include needle and syringe exchange originate in North America, Western Europe, and Australia.

ALTERNATIVE ACCESS TO STERILE NEEDLES AND SYRINGES

Pharmacy Access

Pharmacists can play a key role in preventing HIV infection among IDUs. They can provide advice, including information on safe needle use and substance abuse treatment, and also sell condoms and sterile needles and syringes (Jones and Coffin, 2002). In the United States, many states have "deregulated" or removed laws to allow increased access to sterile needles and syringes through pharmacy sales or physician prescription (Burris et al., 2003). As noted in Chapter 1, syringe prescription laws prohibit the sale of needles and syringes without a prescription and pharmacy regulations may limit the number of syringes a person can purchase at one time (Burris et al., 2003). Relaxation of such laws and regulations governing pharmacy sales of syringes has improved attitudes toward selling to injecting drug users, and increased the number of IDUs who turn to pharmacies for clean injecting equipment (Coffin et al., 2002; Deren et al., 2006).

A well-studied example of the effects of deregulating the availability of syringes through pharmacies is the New York Expanded Syringe Access Demonstration Program (ESAP). This program began in 2001 by allowing pharmacies, health care facilities and practitioners to register and provide up to 10 syringes without a prescription to persons at least 18 years old (Klein et al., 2002). Studies show that IDUs began using pharmacies as a result of this legislation (Deren et al., 2003; Des Jarlais et al., 2002; Fuller et al., 2004).

A serial cross-sectional study by Pouget et al. (2005) found that self-reports of receptive sharing fell significantly—from 13.4 percent in 2001 to 3.6 percent in June 2003 following the legislative change. The number of IDUs obtaining syringes from an ESAP source, mostly pharmacies, rose from 7.5 percent to 25 percent. Deren et al. (2006) examined syringe sources pre- and post-ESAP (n=130). Most drug users who reported obtaining syringes at an NSE before ESAP began continued using that source, although 10 percent reported some use of ESAP. Of drug users who originally relied on unsafe sources, 19 percent reported some ESAP use. Overall, 14 percent of the sample reported some ESAP use.

Other regions of the United States have also experimented with this form of alternative access. Groseclose et al. (1995) examined syringe-

sharing practices before and after Connecticut partially repealed laws requiring prescriptions for needles and drug paraphernalia. Syringe sharing fell from 52 percent to 31 percent (p=0.02) after the change in laws, and 78 percent of IDUs purchased syringes from a pharmacy, compared with 19 percent before.

Singer et al. (1997) surveyed pharmacists in Hartford and its peripheral neighborhoods to study access to over-the-counter syringes. Results showed that 72.2 percent of inner-city pharmacies and 55.6 percent of periphery pharmacies sold syringes without prescription. Some pharmacists cited negative incidents as their reason for requiring a prescription for syringes. Examples of such incidents included improper disposal of used syringes in or near the pharmacy, drug use on pharmacy property, and increased shoplifting.

In a cross-border HIV prevention project for IDUs in China and Vietnam, peer educators distribute sterile needles and syringes directly, as well as vouchers for sterile needles and syringes and other prevention supplies that drug users may redeem at participating pharmacies (Hammett et al., 2005). In Vietnam, the voucher scheme has proved very popular among IDUs: about two-thirds of all needles and syringes provided by the project over 3 years occur through vouchers, with about 8,000 redeemed per month. In China, the vouchers were initially popular, but the novelty appears to have worn off quickly, and most IDUs now prefer to receive needles and syringes directly. This difference between the two countries may reflect differences in concerns about police, the convenience of pharmacy locations, and pharmacists' attitudes toward IDUs (Hammett et al., 2005).

Attitudes of Pharmacists Toward Selling or Providing Syringes

Individual pharmacists can often decide whether to sell syringes without a prescription in areas where it is legal to do so. Many studies have examined the willingness of pharmacists to sell or provide syringes to IDUs, and the factors surrounding their decision. A study in Atlanta found that the personal attitudes and beliefs of individual pharmacists are the most influential factor (Taussig et al., 2002). Some pharmacists fear that IDUs will discard syringes unsafely, and that the presence of IDUs in their pharmacy will be bad for business, while others view syringe access as an HIV prevention method, and see drug dependence as a disease. In Denver, pharmacists viewing syringe sales as a method for preventing disease were more likely to sell syringes to IDUs (Lewis et al., 2002). Concerns also arose in that city, with pharmacists worrying about the effect of IDUs on business and the possibility of discarded syringes near the store.

In Rhode Island, most pharmacists who work in stores that sell non-prescription syringes (n=101) were willing to sell syringes to IDUs (65 percent), were in favor of providing syringe disposal containers (68 percent), and supported providing pamphlets on safe injecting practices (88 percent) (Rich et al., 2002).

Characteristics of IDUs Using Pharmacies for Sterile Needle and Syringe Access

Studies show that IDUs who use pharmacies tend to have lower risk profiles. Miller et al. (2002) compared risk behavior in Vancouver among IDUs who cited pharmacies, fixed NSE, and mobile exchange vans as their primary source of needles and syringes. Pharmacy users had the lowest risk profiles, although they continued to report needle sharing. Studies in Marseille, France (Obadia et al., 1999), and Baltimore, Maryland (Riley et al., 2000), suggest that drug users who rely on pharmacies for equipment are more socially integrated than those who rely on NSEs. As Vlahov (2000) noted, the availability of clean injecting equipment through pharmacies might result in the NSE attracting higher-risk IDUs. Therefore access to pharmacy syringes may influence the findings of studies that compare NSE users with non-users (Ouellet et al., 2004; Gibson et al., 2002; Bruneau et al., 1997).

Physician Prescription Access

The Committee identified one program that offered access to needles and syringes though physician-provided prescriptions. In 1999, a pilot project in Rhode Island aimed to offer medical services, access to syringes, risk reduction counseling, and referrals to other services through syringe prescriptions from physicians (Rich et al., 2004). On the first visit, the physician encouraged an IDU to undergo HIV testing and assessed the need for drug treatment and other services. For IDUs who said they would continue to inject despite advice not to, physicians prescribed up to 100 syringes, providing instructions for proper use and disposal. Participants could then request refills over the phone, and the health clinic made other injecting supplies available. The study found that the syringe prescription program was feasible, and that it attracted a high-risk, underserved IDU population. This type of program served as a link to care, and a basis for substance abuse treatment and other medical and social services. However, the evidence from this pilot study must be considered in light of the limitations associated with a case study.

Supervised Injecting Facilities

Supervised injecting facilities (SIFs)[2] are legally sanctioned and supervised areas where drug users can use pre-obtained drugs in a safe atmosphere under hygienic conditions (Dolan et al., 2000). SIFs are designed to reduce the inappropriate disposal of injecting equipment, keep drug users off the street, reduce fatal and non-fatal overdoses, reduce the transmission of HIV and other bloodborne diseases, and improve access to health and social services. SIFs prohibit drug dealing and provide sterile injecting equipment, referrals to health care and drug treatment, and other services such as meals and showers.

SIFs have long existed in Europe, particularly in the Netherlands, Germany, Switzerland, and Spain (Dolan et al., 2000). In 2003, a pilot SIF opened in Vancouver, with the stipulation that it be vigorously evaluated. The SIF provides injecting equipment and emergency care in the event of an overdose, and an onsite addiction counselor provides referrals to treatment programs. The evaluation examined risk behavior, blood-borne infection transmission, overdoses, and the use of health services among a cohort of SIF users (Wood et al., 2004a).

In the first 18 months of the program, 4,764 individuals registered with the SIF (Tyndall et al., 2006). Heroin was injected 46 percent of the time. Although cocaine use is generally characterized by repeated injections, and only one injection is allowed per SIF visit, cocaine was injected 37 percent of the time. In a 12-month period, the SIF made 2,171 referrals—37 percent to addiction counseling (Tyndall et al., 2006).

A cross-sectional study based on the Vancouver SIF examined factors associated with syringe sharing (Kerr et al., 2005). Logistic regression analyses found that use of the SIF was independently associated with a three-fold reduction in syringe sharing (AOR=0.30; 95% CI: 0.11–0.82; p=0.02).

In terms of unintended consequences, a study by Wood et al. (2004b) examined injecting-related public disorder problems before and after the opening of the Vancouver SIF. The 12-week period after the SIF opened was independently associated with reductions in the number of IDUs injecting in public, and the number of discarded syringes and other paraphernalia. Wood et al. (2006a) examined crime rates in the surrounding area during the year before and the year after the SIF opened. The study relied on police records of drug trafficking, assaults and robberies, and vehicle break-ins and thefts. The study found no differences between the 2 years

[2]Supervised injecting facilities are also known as drug consumption facilities, safer injecting facilities, supervised injecting centers, and medically supervised injecting centers.

with respect to these crimes. Similarly, a study by Wood and colleagues (2006b) showed that SIFs were unlikely to result in reduced use of addiction treatment services. In multivariate analyses, an average of at least weekly use of the SIF (relative hazards=1.72; 95% CI: 1.25–2.38) and contact with the SIF's addiction counselor (relative hazards=1.98; 95% CI: 1.26–3.10) were both independently associated with faster entry into a detoxification program.

SIFs are known as medically supervised injecting centers (MSIC) in Australia. In 2003, a report evaluating the MSIC in Kings Cross (MSIC Evaluation Committee, 2003) concluded that:

- There were no changes in the number of heroin overdoses in the community.
- The MSIC made referrals for drug treatment.
- There was no increase in risk of blood-borne virus transmission.
- There was no increase in crime.
- The majority of the community accepted the presence of the MSIC.

A review study by Dolan et al. (2000) summarized the literature on SIFs in the Netherlands, Germany, and Switzerland. This review referenced studies showing a shift in public drug use and a general reduction in the visibility of the drug scene, as well as improved health of clients owing to contact with health and social services onsite and through referrals. Less evidence exists related to overdoses, although SIFs have reported no overdose deaths. Similarly, no studies have linked SIFs to HIV transmission, but reductions in risk behavior such as needle sharing and condom use have occurred among SIF clients.

Vending Machines

Syringe vending machines work like other types of vending machines, except that they accept contaminated syringes and dispense sterile syringes in exchange (Obadia et al., 1999). The Committee identified two studies from France and one study from Germany that examined the characteristics of users of such vending machines, and the machines' usefulness in providing access to sterile syringes (Obadia et al., 1999; Moatti et al., 2001; Stark et al., 1994). One other study examined the feasibility of a pilot syringe vending machine project in a prison in Germany (Heinemann and Gross, 2001). All these studies showed that IDUs will use vending machines as a source of sterile needles and syringes, when available. None of these studies examine the effect of syringe vending machines on HIV-related risk behavior.

Obadia et al. (1999) collected questionnaires from 343 IDUs who ob-

tained their syringes from 32 pharmacies, 4 NSEs, and 3 vending machines in Marseille, France. Two-thirds (n=222) of respondents reporting the use of vending machines said that their main reasons were that syringes were free of charge and that the machines were available at all times. Primary users of vending machines (21.3 percent of the total sample) were younger and less likely to have been in drug treatment or to have engaged in HIV-related risk behavior in the past 6 months. This study concluded that despite the presence of other means of sterile needle and syringe access, vending machines attracted a regular portion of the IDU population that tended not to use the other services. There was no evidence that the vending machines were being abused. As compared to IDUs reporting predominant use of NSE or pharmacies for sterile needle and syringe access, duration of drug use did not last longer among IDUs reporting predominant use of vending machines (Obadia et al., 1999).

Based on the above evidence regarding pharmacy sales, physician-based prescriptions, supervised injecting facilities, and vending machines, the Committee concludes:

Conclusion 3-9: There is moderate evidence that the elimination of criminal penalties for possessing needles and syringes—and the enhancement of legal access via pharmacy sales, voucher schemes, and physician prescription programs—are alternative avenues for making sterile needles and syringes available to IDUs. Evaluations of these strategies have been conducted in the United States, and have focused on assessing the acceptability of such programs by drug users, pharmacists, and physicians. A few studies have examined the impact on drug-related HIV risk, and found suggestive evidence of a reduction.

Conclusion 3-10: The evidence regarding supervised injecting facilities and vending machines—while encouraging—is insufficient for drawing conclusions on the effectiveness of these interventions in reducing drug-related HIV risks among IDUs.

Recommendations for Sterile Needle and Syringe Access Programs

Recommendation 3-1: Given consistent evidence that multicomponent HIV prevention programs that include sterile needle and syringe access reduce drug-related HIV risks, such programs should be implemented where feasible. Sterile needle and syringe access may include needle and syringe exchange or the legal, accessible, and economical sale of needles and syringes through pharma-

cies, voucher schemes, and physician prescription programs. Other components of multi-component HIV prevention programs may include outreach, education in risk reduction, HIV voluntary counseling and testing, condom distribution, bleach distribution and education on needle disinfection, and referrals to substance-abuse treatment and other health and social services.

Recommendation 3-2: Multi-component HIV prevention programs that include sterile needle and syringe access should:

- **Maximize their accessibility to the largest number of IDUs by using multiple access points and methods of delivery.**
- **Focus on reducing sex-related HIV risk behavior.**
- **Actively refer IDUs to other services, such as substance abuse treatment, HIV voluntary counseling and testing and, if appropriate, antiretroviral treatment for HIV.**
- **Focus additional efforts on preventing hepatitis C infection, such as by providing sterile cotton swabs, alcohol wipes for cleaning injection sites, sterile water, cookers, and other disinfection supplies.**
- **Incorporate strong program and component evaluations, and where feasible, include comparison populations or regions.**

DISINFECTION PROGRAMS

Research on disinfection of injecting equipment may entail either laboratory (efficacy) studies or field (effectiveness) studies. A previous review by the National Research Council and the Institute of Medicine, *Preventing HIV Transmission: The Role of Sterile Needles and Bleach* (NRC and IOM, 1995) discussed laboratory studies extensively. Several laboratory studies published since that report support the panel's findings (Abdala et al., 1999, 2001; 2004; Contoreggi et al., 2000; Druce et al., 1995; Van Bueren et al., 1995; Weber et al., 1999). The next section briefly summarizes the report and the more recent lab studies, although these types of studies are difficult to compare because of differences in their protocols and experimental conditions. Because field studies of disinfection programs are more relevant to the charge of this Committee, the ensuing section discusses those studies more completely.

Laboratory Studies

A study by Newmeyer (1988) identified five essential features of disinfection techniques for IDUs. According to the author, the technique should: (1) be quick, preferably less than 60 seconds; (2) be inexpensive; (3) use

materials conveniently available; (4) be safe for the user and the injection equipment; and (5) be effective in neutralizing viruses.

Several early studies examined different disinfectants, such as bleach, hydrogen peroxide, isopropyl alcohol, and common household products (Spire et al., 1984; Martin et al., 1985; Resnick et al., 1986). These studies found that bleach was the most feasible disinfectant because of its wide availability and low cost, and because accidental injection would not greatly harm drug users (Froner et al., 1987). A bleach solution loses potency over time, and more quickly when exposed to sunlight, oxygen, and heat (NRC and IOM, 1995). Contact time, volume of blood, and the presence of other matter, such as clotted blood in syringes, also affect efficacy. Although the optimal exposure time for inactivating HIV is 30 seconds, laboratory studies have found that variations on this amount of time are acceptable.

Shapshak and colleagues (1994) obtained blood from HIV-1 infected IDUs, to test the effectiveness of bleach as a disinfectant for needles and syringes. Results showed that undiluted household bleach can inactivate HIV-1 in both clotted and unclotted blood—allowed to stand at room temperature for different periods, including 3, 6, 18, and 24 hours—after an exposure time of 30 seconds. Ten percent bleach did not inactivate HIV-1 in clotted blood after an exposure time of 30 seconds, and undiluted bleach was not effective at an exposure time of 15 seconds. However, critics assert that the volume of blood in the syringes was greater than would normally occur.

Druce et al. (1995) similarly found that when contaminated syringes were allowed to stand at room temperature for 3 hours, undiluted bleach inactivated or removed cell-associated HIV after 30 seconds. Another study by Newmeyer et al. (1990) found that undiluted bleach eradicated cell-free HIV after an exposure time of 60 seconds.

More recently, in 2001, Abdala and colleagues simulated common drug injection practices, to prepare syringes for a study. Of unrinsed syringes stored for about 1 day, 86 percent yielded viable HIV-1, with the volume of blood in the syringe affecting the outcomes. Rinsing the syringes once with water significantly lowered recovery of HIV-1, and rinsing them more often decreased recovery even more. Rinsing the syringes once with 10 percent diluted bleach also significantly reduced recovery—equivalent to a single rinse with water. Of 153 syringes rinsed with undiluted bleach, in contrast, HIV-1 was recovered from only 1. (Contact time for all rinses was about 5 seconds.)

Contoreggi et al. (2000) showed that high concentrations of bleach inhibit in-vitro replication of HIV-1 and reduce the viability of target cells. Lower concentrations of bleach in the cell-culture medium did not reduce the viability of target cells, and appeared to allow HIV-1 infection and replication.

Studies have also examined the efficacy of other common disinfectants. Flynn et al. (1994) found that liquid dish detergent and rubbing alcohol may be viable alternatives when bleach is not available. However, the study performed only a small number of repetitions, and Abdala et al. (2004) found that dish detergent does not fully disinfect syringes. Improperly stored bleach—stored at 37°C and exposed to light—and rubbing alcohol performed better than water and other liquids but worse than properly stored 10 percent bleach.

Bleach does fade the numbers on the syringe barrel that indicate dose levels, and could corrode rubber inside the syringe (Newmeyer, 1988). Flynn et al. (1994) found that relatively few rinses of undiluted bleach can damage syringes. Morgan (1992) reported a case of a 31-year-old man who injected less than 1 milliliter of bleach and then experienced transient left-sided chest pain and vomiting, but no serious complications.

Based on this evidence, the Committee concludes:

Conclusion 3-11: Strong evidence from laboratory studies shows that undiluted bleach can inactivate HIV in injecting equipment, and is more efficacious than other tested disinfectants. Storage conditions, contact time, volume of blood, and the presence of other matter influence the efficacy of bleach as a disinfectant.

Field Studies

Although laboratory studies show that undiluted bleach inactivates HIV after an exposure time of 30 seconds, the evidence supporting the effectiveness of bleach disinfection in the field is weak. The Centers for Disease Control and Prevention endorses a procedure for using bleach to cleanse injecting equipment (see Box 3.2). Despite wide agreement on this technique, it is unclear what research, if any, has been performed to examine alternative options for effective bleach disinfection that would be simpler or more acceptable to IDUs. Later in this chapter, the Committee calls for more research on developing simple and effective disinfection techniques as well as strategies for increasing the uptake of these techniques. The Committee did not identify any studies examining the effectiveness of alternative disinfectants, despite the fact that bleach is not available or acceptable in certain settings.

Four studies have shown that IDUs fail to comply with the recommended procedures. McCoy and colleagues (1994) evaluated the recall and performance of a common bleach disinfection procedure. This entails completely filling the syringe with bleach twice, and then filling the syringe completely with water twice, without returning the used bleach or water to the source containers. During follow-up 6 to 12 months after IDUs (n=450)

BOX 3-2 Instructions for Disinfecting Syringes

- Fill the syringe with clean water and shake or tap.
- Squirt out the water and throw it away. Repeat until there is no visible blood in the syringe.
- Completely fill the syringe with fresh, full-strength household bleach.
- Keep it in the syringe for 30 seconds or more.
- Squirt it out and throw the bleach away.
- Fill the syringe with clean water and shake or tap.
- Squirt out the water and throw it away.

SOURCE: CDC (2004).

were taught the procedure, more than 90 percent performed the basic steps. However, only 43.1 percent completely filled the syringe with bleach, and only 35.8 percent did so at least twice.

Gleghorn and colleagues (1994) measured syringe-cleaning strategies among IDUs in Baltimore by interviewing them and videotaping a demonstration of their most recent injection. Of the 146 IDUs who reported cleaning their needles, 85 (58 percent) used full-strength household bleach. Of the IDUs who did not use full-strength bleach, 90 percent used water alone. Eighty percent of the 85 bleach users recorded a total contact time of less than 30 seconds, and only 30.6 percent filled the syringe at least halfway. The authors noted that the median contact time per flush was approximately 10 seconds, indicating that drug users might achieve the minimum contact time of 30 seconds if they were encouraged to perform at least three flushes.

Carlson et al. (1998) compared baseline needle-cleaning practices with those after an intervention, with follow-up occurring 2 to 4 weeks and 6 months later. Mean exposure time rose from 13.8 seconds at baseline (n=541) to 21.1 seconds at 6-month follow-up ($t=2.98$; $p<0.05$). Only 30.3 percent of IDUs kept bleach in the syringe for at least 30 seconds at the 6-month follow-up.

In 1987, Chaisson et al. evaluated a program in San Francisco in which outreach workers distributed vials of 5.25 percent sodium hypochlorite (bleach) and instructions on sterilizing equipment. The study compared rates of needle and syringe disinfection in 1985 with those in 1987, one year after the program began. In both years, 71 percent of subjects reported sharing needles. In 1987, (n=172), 47 percent of sharers reported that they usually or always used bleach to clean their equipment, compared with only 6 percent who reported doing so in 1985 (n=152). The prevalence of HIV

among IDUs in treatment also rose, from 10 percent in 1985 to 15 percent in 1987.

Effect on HIV Seroconversion

Three nested case-control studies have examined the impact of reported bleach use on HIV seroconversion among IDUs. These studies found that bleach use offered little protection against HIV infection. In Baltimore, Vlahov et al. (1991) compared 22 black heterosexual HIV seroconverters with 95 persistent HIV-seronegatives matched on gender, use of cocaine, date of entry into the study, and duration of follow-up. The study found that bleach use had a limited protective effect on HIV seroconversion. The odds ratio for seroconversion among IDUs reporting disinfection all the time was 0.77, compared with an odds ratio of 0.91 among those reporting disinfection some of the time. Shooting gallery users reporting frequent use of disinfectant had an odds ratio of seroconversion of 0.63. In a similar study, Vlahov et al. (1994) found that IDUs reporting the use of disinfectant all the time had an odds ratio of seroconversion of 0.87 (95% CI: 0.32–2.37), compared with those reporting no use of disinfectants.

A nested case-control study by Titus et al. (1994) evaluated the efficacy of bleach disinfection of needles and syringes among IDUs in preventing HIV infection. Cases included 16 HIV seroconverters who reported injecting with shared or used equipment in the 6 months before their first HIV-seropositive visit. Controls included 89 HIV-negative IDUs who reported injecting with shared or used equipment, and who were seen within 6 months of the seroconversion of the index case. Risk factors (based on univariate analyses) included a history of sexual intercourse with an HIV-seropositive partner, and frequency of speedball injection (mixed heroin and cocaine). Bleach use was not associated with a decreasing odds for HIV seroconversion. In multiple logistic regression analysis, the frequency of bleach use was not significant (likelihood ration p-value=0.07) after adjusting for sex with an HIV-seropositive partner, speedball injection frequency, frequent recall, and gender.

Because HCV is more easily transmitted than HIV, strict compliance with disinfection procedures is even more important. In a nested case-control study, Kapadia et al. 2002 examined whether disinfection with bleach protects people from hepatitis C virus seroconversion. Participants who reported using bleach all the time had an odds ratio for HCV seroconversion of 0.35 (95% CI: 0.08–1.62), while those reporting bleach use some of the time had an odds ratio of 0.76 (95% CI: 0.21–2.70), compared with those reporting no bleach use.

These studies suggest that while bleach and other disinfectants are

efficacious in eradicating HIV in injecting equipment in controlled laboratory settings, the effectiveness of disinfection programs is not convincing in uncontrolled field settings. This may be due partly to inadequate education on proper cleaning techniques or their inherent complexity and time-consuming nature. As discussed in Chapter 1, injecting drug users can follow a hierarchy of steps to reduce their HIV risk. The best approach is to stop using drugs. If a drug user is unable to stop using or injecting drugs, the use of new injecting equipment for each injection will help prevent HIV transmission. Disinfecting used equipment with bleach is an option when new equipment is not available, because that procedure can decontaminate needles and syringes if done properly.

Conclusions and Recommendation for Disinfection Programs

Conclusion 3-12: If used according to the guidelines of the Centers for Disease Control and Prevention, the National Institute on Drug Abuse, and the Center for Substance Abuse Treatment, there is strong evidence that undiluted bleach can be an effective HIV prevention strategy for injecting drug users who share needles and syringes.

Conclusion 3-13: Strong evidence from field studies shows that, in practice, IDUs do not correctly use bleach, and that they fail to properly disinfect syringes.

Recommendation 3-3: Because field studies have shown that drug users often fail to properly disinfect injecting equipment, concerted effort should be made to increase the uptake of effective procedures for disinfecting shared equipment. IDUs should rely on disinfection to prevent HIV and HCV infection only when they cannot stop injecting or do not have access to new, sterile injecting equipment. Undiluted bleach is the most effective disinfectant. However, in some settings, bleach may not be available or acceptable for disinfecting injection equipment, and IDUs may use or need alternative disinfectants.

OUTREACH AND EDUCATION

To evaluate the effectiveness of outreach programs in preventing HIV infection, the Committee considered studies identified by its literature review (see Appendix B). This analysis focused on the effect of outreach on (1) drug-related risk behavior; (2) sex-related risk behavior; (3) HIV incidence; and (4) links with care.

Drug-Related Risk Behavior

Evidence associates outreach with reductions in drug-related risk. In 1998, a review of published outcome data regarding outreach-based HIV prevention efforts concluded that they have been effective in reaching out-of-treatment IDUs and spurring behavioral change (Coyle et al., 1998). That review examined 36 studies, most of which were observational or quasi-experimental and were derived from research supported by the National Institute of Drug Abuse (NIDA) of the United States. Nineteen of the 36 studies were evaluations of interventions from the National AIDS Demonstration Research Program (NADR), which began at NIDA in 1987 and was designed to facilitate the implementation of HIV prevention outreach and intervention initiatives throughout the United States (Coyle et al., 1998). Projects were focused on reaching out-of-treatment drug users and their sexual partners, and employed former drug users and other community members to recruit and retain people in the intervention programs (Coyle et al., 1998). Twelve of the 36 studies were evaluations from interventions of the successor of NADR, the Cooperative Agreement for AIDS Community-Based Outreach/Intervention Research (Coyle et al., 1998).

Outreach activities through NADR included basic risk reduction activities such as literature on HIV prevention and services, distribution of condoms and bleach kits, and referrals to services including drug treatment (Coyle et al., 1998). Enhanced outreach interventions also included HIV testing and counseling and bleach and condom demonstrations. Study participants were often randomly assigned to either basic outreach services or basic outreach plus enhanced outreach services. In the Cooperative Agreement studies, interventions were standard across all sites. Outreach was conducted a maximum of five times and provided HIV education and service referrals, and condom and bleach distribution. HIV testing and counseling was a standard follow-up activity that included demonstrations of condom and bleach use. The education sessions promoted messages that covered the hierarchy of risk reduction (stop using drugs; stop reusing injecting equipment; disinfect reused injecting equipment) (Coyle et al., 1998).

The studies consistently reported that after an outreach intervention, significant declines occurred in self-reported injection drug use (10 of 11 studies), injection frequency (17 of 18 studies), reuse of needles and syringes (16 of 20 studies), and reuse of other equipment such as cookers, cotton, and rinse water (8 of 12 studies) (Coyle et al., 1998). The studies also showed significant effects in protective behaviors such as more frequent disinfection of needles, entry into drug treatment, and increases in condom use. Although the studies in this review did not have control groups, most studies of NADR and Cooperative Agreement interventions were

based on pre-test and post-test designs of a specific group. The comparison of behaviors at baseline to those at follow-up established a time sequence between intervention and outcome. In addition, the observed effects of the interventions were similar across evaluations more often than not (Coyle et al., 1998). To corroborate the self-reports of drug-related risk behavior, NADR and Cooperative Agreement investigators used urinalysis and visual examination of recent needle injection. There were no tools available to corroborate reports of sex-related risks (Coyle et al., 1998).

A later review article by Needle and colleagues (2005) updated the 1998 review and confirmed findings that outreach results in self-reported reduction in HIV-related risk behavior. This review lays out the origins and evolution of community-based outreach models starting from the early 1980s when outreach was characterized by repeated and time-intensive contact with IDUs by "insiders" to the IDU population. In the 1990s, peer-driven models were designed to focus on IDU networks as a method to reduce individual IDU risk. Many recent outreach models rely on recruiting people from IDU concentrated areas and encouraging them to use their residences for services and to provide the means for behavior change. Outreach services are also linked to voluntary testing and counseling and HIV treatment services. This review reported its findings in relations to three questions: (1) Is outreach an effective strategy for reaching hard to reach, hidden IDU populations and providing the means for changing behavior? (2) Do a significant proportion of IDUs receiving outreach-based interventions reduce their HIV risk behaviors—drug using, injecting equipment use, and sexual—and adopt safer behaviors? (3) Are changes in behaviors associated with lower rates of HIV infection among IDUs? The review concluded that evidence from more than 40 studies indicate that community-based outreach reaches hidden populations and provides the means for behavior change among IDUs, including reduction of drug use, reduction of syringe and other equipment sharing, and if referrals are available, increased use of drug dependence treatment and voluntary counseling and testing.

Discerning which intervention component is responsible for which outcome is often difficult, especially when individual programs include numerous interventions that occur simultaneously. A study by Colon (1995) in Puerto Rico showed that secular trends unrelated to the direct effects of outreach accounted for a significant reduction in reported risk. However, later trends in sharing of cookers and bleaching of needles showed shifts that the secular trends could not account for. The authors concluded that the outreach exerted a significant but partial effect on behavioral risk associated with drug injection, and had no effect on sexual risk behavior. A study by Neaigus et al. (1990) of the AIDS Outreach Project in New York

City—which provided information and anonymous HIV testing to street-recruited IDUs—also found that external trends could not account for reductions in risk.

Sex-Related Risk Behavior

Evidence that outreach exerts a positive impact on sex-related HIV risk behavior among IDUs is less substantial. Most outreach focuses on limiting drug-related risk, despite the fact that sexual risk behavior among IDUs raises the odds that they will transmit HIV to the general population (Semaan et al., 2002). A review by Coyle et al. (1998) found that 16 of 17 studies showed an increase in self-reported condom use or a decrease in self-reported unprotected sex after outreach. The authors note, however, that a large percentage of IDUs continued to practice high-risk sexual behavior. The review by Needle et al. (2005) showed that outreach can increase condom use, but that as compared to drug-related risk, smaller changes were seen in sexual risk reduction.

Another review by Empelen et al. (2003) focused mostly on psychosocial interventions, but did examine three studies of outreach and community-level interventions. Two (Jamner et al., 1997; Rietmeijer et al., 1996) of these three studies found changes in sexual behavior—such as self-reported condom use and number of sex partners—among participants in an intervention, compared with control groups, while one study did not find any risk reduction (Collins et al., 1999).

A meta-analysis by Semaan et al. (2002) showed that some interventions have lowered sexual risk among IDUs, including outreach based on multiple theories and strategies, peer interventions, and skills training. A study of network-oriented peer outreach suggests that interventions with an emphasis on social roles and identity can reduce injection risk behavior and increase condom use with casual sex partners (Latkin et al., 2003).

Effects on HIV Incidence

The Committee found one study that directly examined the impact of outreach on HIV incidence. In a prospective cohort study, Wiebel (1996) monitored trends in HIV risk behavior and seroconversion among IDUs receiving street-based outreach in Chicago from 1988 to 1992. The study found that HIV seroconversion fell from 8.4 to 2.4 per 100 person-years. Drug-related risk behavior also declined from 54 percent at baseline to 14 percent in the final year of follow-up. Seroconversion was associated with injection risk behavior (RR=9.8).

Outreach and Education in High-Risk Countries

While there are many studies that provide descriptions of outreach and education activities in high-risk countries (see Box 3.3 for an example), the Committee identified only three studies examining the effectiveness of outreach and education as HIV prevention for IDUs. A study by Peak et al. (1995) in Kathmandu, Nepal, measured changes in self-reported HIV risk behavior and HIV seroprevalence among IDU clients of a comprehensive outreach program from 1991 to 1994. The program distributed clean injecting equipment, condoms, and bleach, and provided education, counseling, and primary health care. Results showed that indictors of unsafe injecting fell and knowledge of HIV rose, while indicators of unsafe sex did not change. HIV seroprevalence remained low, at 1.6 percent in 1991 and 0

BOX 3-3 An Example of Outreach in India

Churachandpur is a small town in the northeastern state of Manipur that is currently home to about 600 to 800 IDUs. The town's six drug treatment centers offer abstinence-based spiritual and 12-step programs.

Leaders of an outreach project believed that before it could begin, they needed buy-in from the community, including law enforcement and religious leaders. Toward that end, project leaders created an advisory committee chaired by the local police commissioner. Police support for the program increased, and outreach workers were not harassed once the project began. Project leaders also met with religious leaders and gave them factual information on HIV/AIDS. Although the attitude of the religious leaders toward drug users did not change, they did appreciate the importance of the outreach intervention in preventing HIV and supported it. Project leaders also built awareness of HIV/AIDS among families and friends of IDUs, local nongovernmental organizations, and health professionals.

Outreach workers were chosen to represent the town's many ethnic groups, and the majority had a history of injecting drug use. These workers were trained in the basic facts of HIV, the importance of preventing transmission among IDUs and their partners, how to deliver prevention messages, when and where to refer IDUs for drug treatment, and safety and security.

Outreach workers were assigned to areas identified as gathering places for IDUs. On first contact with IDUs, workers explained the project, while at later meetings they presented prevention messages and distributed kits, including bleach (and instructions for use), cookers, clean water, cotton, and condoms. Within a year, the project had distributed about 4,000 kits and reached some 750 IDUs. Outreach workers also provided referrals for medical services and drug treatment, although the area lacked health care services generally, and the closest HIV voluntary counseling and treatment center was 60 kilometers away.

SOURCE: Hangzo et al. (1997).

percent in 1994. Later studies found that HIV prevalence among IDUs in Kathmandu grew rapidly, from 0 percent in 1995 to 40 percent in 1997, and to 68 percent in 2002 (Oelrichs, 2000; UN Nepal Information Platform, 2005).

Chen and Liao (2005) considered a culture-based model that places health education in the context of Chinese ethics. Pre- and post-test data from a pilot study showed that such a program among female IDUs (n=100) increased knowledge of HIV/AIDS, increased condom use, and decreased needle and syringe sharing. Kumar et al. (1998) examined the effectiveness of community-based outreach in reducing risk behavior for HIV transmission in two locations in Madras, India. Frequency of needle use and sharing declined significantly (p=0.01) among IDUs at outreach locations, compared with IDUs at control locations with no outreach services. Approximately 30 percent of IDUs from outreach locations always cleaned syringes and needles before use, compared with 10.3 percent of control IDUs. The two groups did not differ significantly in their sexual risk behavior.

Links to Health and Social Services

One study showed that outreach increases drug users' entry into treatment programs (Rowden, 1999). Participants were recruited from 1 of 12 HIV Outreach Demonstration Projects funded by the U.S. Center for Substance Abuse Treatment. Clients from hard-to-reach groups were more likely to enter treatment for substance abuse through outreach programs than through treatment-specific recruiting. Outreach was particularly effective in reaching drug users earlier in the cycle of abuse. A review by Coyle et al. (1998) reported that six of seven studies found that outreach participants entered drug treatment. The review by Needle et al. (2005) points out that recent data from a multi-site (12 cities) study from 1995–2000 in the United States shows that of IDUs reached by the outreach intervention, 68 percent were referred to drug treatment of whom 41 percent entered treatment.

Conclusions and Recommendations on Outreach

Conclusion 3-14: Modest evidence from several studies and reviews from developed countries—most with weak study designs—shows a degree of consistency in finding that outreach and education reduces self-reported drug-related risk behavior. There is limited evidence that outreach can reduce self-reported sex-related HIV risk behavior.

Conclusion 3-15: There is moderate evidence that outreach is an effective strategy for providing education on preventing HIV transmission, and referrals to services, for hard-to-reach populations of IDUs.

Recommendation 3-4: Outreach services should be made available to provide education on risk reduction and links to sterile needle and syringe access programs, drug treatment, and medical and social services for hard-to-reach IDUs.

FUTURE RESEARCH

The Committee identified several gaps in the evidence base for policymaking and program building. First, there is limited evidence on the impact of sterile needle and syringe access and outreach and education on reducing sexual risk. Additional research is needed to identify the most effective sexual risk reduction strategies for IDUs, and to determine how to successfully integrate these strategies into multi-component programs and outreach and education.

Second, few studies have specifically evaluated whether HIV prevention programs that include needle and syringe exchange lead to unintended consequences such as increases in new drug users, expanded networks of high-risk users, more discarded needles in the community, and changes in crime trends. Future research should specifically evaluate these unintended outcomes, and—if found—develop strategies for addressing them.

In addition, while laboratory studies have shown that undiluted bleach is an effective disinfection agent, field studies show that IDUs often fail to properly use bleach to disinfect equipment, thereby putting them at risk for acquiring HIV. More research is needed on alternative bleach disinfection techniques that are both simple and acceptable, and on the best methods for educating IDUs on those techniques. The Committee is also aware that in some countries, bleach is not available or acceptable for use. While alternative disinfectants have been examined in laboratory settings, the Committee did not identify any studies that examine the effectiveness of alternative disinfectants (e.g., water, alcohol, hydrogen peroxide, detergent) in field settings, and calls for more research in this area.

Furthermore, in light of the persistently high incidence of HCV among NSE participants, more research is also needed on the impact of NSE and related prevention services on the incidence of hepatitis C among IDUs. Such research should particularly focus on new injectors, and assess whether enhanced programs that provide specific information on reducing HCV risk—and that provide other clean materials such as alcohol swabs, sterile cotton, and water—reduce the incidence of HCV.

Finally, studies show that multi-component prevention programs that include needle and syringe exchange are associated with reductions in drug-related HIV risk behavior. The Committee believes that multi-component programs that include NSE are likely to add value to a national HIV prevention program, but that existing research does not allow us to disentangle the specific contribution of each component. The individual components probably have different levels of effectiveness, and they may interact in ways that are not fully understood. A full understanding of each intervention component may highlight those that do not add substantial value in the presence of other interventions, and that are associated with unanticipated effects. In some cases the effects may be synergistic. This issue is important from a policy perspective because elements of these multi-component prevention programs can be resource intensive.

Further research is needed to help identify the most effective and cost-effective combination of programs that is feasible for high-risk countries. While these questions could be addressed in several ways, a community randomized trial would be the most rigorous approach (see Box 3.4 for an explanation of community randomized trials). Because of the complex nature of community randomized trials, the Committee provides an overview of potential trial design and implementation challenges in Appendix E. While the call for further research may seem to contradict the advice to launch multi-component programs that include NSE now, that call reflects a balance between the urgent need to prevent HIV infection and the responsibility to do so in the most ethical, effective, and cost-effective manner possible. Imperfect knowledge is not a defense against inaction in this case, and the wait for the results of further research should not hinder the implementation of multi-component approaches, however incompletely understood.

Recommendation 3-5: The Committee recommends that additional research focus on:

- **The impact of outreach and education and multi-component programs that include sterile needle and syringe access on sexual risk reduction.**
- **Integration of effective strategies for reducing sexual risk behavior and sexual transmission of HIV into multi-component programs that include sterile needle and syringe exchange and outreach and education.**
- **The potential unintended consequences of HIV prevention programs that include needle and syringe exchange, such as increases in new drug users or in discarded needles in the community, and strategies to address such problems, if they are found.**

BOX 3-4 Community Randomized Trials

In a community randomized trial, some communities receive certain added interventions while other communities awaiting such interventions serve as comparison sites (often called "controls"). A stepped-wedge design would be most appropriate for a community randomized trial of multi-component HIV prevention programs. This design involves sequential rollout of an intervention (whereby intervention components are added to a standard package) in participating communities over time. Areas that are yet to receive a specific intervention serve as controls for the intervention area(s). This design is particularly relevant where an intervention may do more good than harm (making a factorial design, in which certain participants do not receive the intervention, unethical). Such a design is also appropriate where, for logistical, practical, or financial reasons, a program cannot simultaneously deliver an intervention to all participants (Gambia Hepatitis Study Group, 1987).

A "no treatment" or "minimal treatment" control arm would be inappropriate. Instead, control communities should have a substantial prevention program equaling or exceeding that already available. For example, in evaluating the effectiveness of a needle and syringe exchange component, investigators might provide a basic package of services, such as voluntary HIV counseling and testing to promote behavioral change, education on needle disinfection, and referrals to health services and drug treatment in both the control and experimental communities. Needle and syringe exchange could then be added in the experimental communities as part of a sequential rollout across all trial sites.

A community randomized trial makes particular sense for injecting drug users because they may share the same drug-using network and compare their treatment experiences. Thus randomizing participants on an individual basis could create situations where the control group could not be insulated from the intervention group, potentially contaminating the control regimen and blunting the study's ability to detect important differences.

A community randomized trial could measure actual HIV incidence as a primary outcome. The trial would also represent an opportunity to evaluate the impact of multi-component prevention programs on HCV transmission. Secondary outcomes might include subjective and objective measures of risk behavior, including drug-related behavior (such as self-reports of needle sharing and needle disinfection) and sexual behavior (such as self-reports of condom use). Secondary outcomes might also include potential harm at the individual and community level (such as an increase in discarded needles or recruitment of new users). The study could also collect data on program costs and cost-effectiveness, to inform decisions on how best to allocate resources. A formative evaluation component could shed light on the best strategies for implementing the prevention program. See Appendix E for more detail on design and implementation issues related to community randomized trials.

- **Identifying the simplest, most acceptable effective disinfection techniques using bleach, and the best methods for educating IDUs on these techniques.**
- **The effectiveness of alternative disinfectants in field settings, particularly in countries where bleach is not available or acceptable.**
- **Identifying effective strategies for preventing HCV among IDUs.**
- **The costs and contributions of individual elements of multi-component programs that include needle and syringe exchange on HIV-related risk behavior and HIV incidence (see Box 3.4 and Appendix E).**

CONCLUSION

For injecting drug users who cannot gain access to treatment or are not ready to consider it, multi-component HIV prevention programs that include sterile needle and syringe access reduce drug-related HIV risk behavior such as self-reported sharing of needles and syringes, unsafe injecting and disposal practices, and frequency of injection. Avenues of sterile needle and syringe access may include needle and syringe exchange; the legal sale of needles and syringes through pharmacies, voucher schemes, physician prescription programs, and vending machines; or supervised injecting facilities. Needle and syringe access is often part of a multi-component HIV prevention program. Other elements of multi-component programs may include outreach, education in risk reduction, HIV voluntary counseling and testing, condom distribution, bleach distribution and education on needle disinfection, and referrals to substance abuse treatment and other health and social services.

Participation in multi-component HIV prevention programs that include needle and syringe exchange is associated with a reduction in self-reported drug-related HIV risk behavior among IDUs. Such behavior includes self-reported sharing of needles and syringes, safer injecting and disposal practices, and frequency of injection. Sterile needle and syringe access is not primarily designed to address sex-related risk behavior, and this issue has not been well studied. The existing evidence is insufficient to determine the effectiveness of programs that include needle and syringe access in reducing sex-related risk. The Committee calls for more research to determine the impact of such programs on sex-related risk, and on integrating effective strategies for reducing sexual risk behavior and sexual transmission of HIV into multi-component programs that include sterile needle and syringe access.

The evaluation of strategies to eliminate criminal penalties for possess-

ing needles and syringes—and enhance legal access via pharmacy sales, voucher schemes, and physician prescription programs—have focused on assessing the acceptability of such programs by drug users, pharmacists, and physicians. A few studies have examined the impact on drug-related HIV risk, and found suggestive evidence of a reduction. The evidence regarding supervised injecting facilities and vending machines—while encouraging—is insufficient for drawing conclusions on the effectiveness of these interventions in reducing drug-related HIV risks among IDUs.

As with drug treatment, a common concern is that sterile needle and syringe access may produce unintended results, including more new drug users, expanded networks of high-risk users, more frequent injection, and more discarded needles in the community. While few studies have specifically examined such outcomes, studies to date have not found evidence of negative effects. More research is needed on potential unintended consequences of HIV prevention programs that include needle and syringe access, and strategies to address such problems if they are found.

Undiluted bleach can inactivate HIV on injecting equipment in the laboratory, and in the field if used according to guidelines. However, in practice, injecting drug users do not use bleach correctly, so programs that distribute bleach should also educate drug users on proper techniques. In some countries, bleach is not available or acceptable, and it may be necessary to use other disinfectants. Drug users should rely on such methods only when they cannot stop injecting, or do not have access to new equipment. More research is needed to identify the simplest and most acceptable effective disinfection techniques using bleach and the best methods for educating IDUs on these techniques as well as the effectiveness of alternative disinfectants in field settings, particularly in countries where bleach is not available or acceptable.

Outreach-based efforts to prevent HIV transmission—which may direct drug users to needle and syringe exchange, for example—are associated with reductions in drug-related risk behavior, including injection frequency and sharing of injection equipment. Outreach is effective in linking hard-to-reach IDUs with drug treatment and other health and social services. The impact of outreach on sex-related HIV risk behavior is less clear and more research is needed to study this impact. More research is also needed to determine the best way to integrate effective strategies for reducing sexual risk behavior and sexual transmission of HIV among IDU into outreach and education programs.

Although questions remain about the contribution of individual elements of multi-component programs that include sterile needle and syringe access and outreach and education on risk behavior and actual HIV incidence, the report recommends that high-risk countries act now to implement such programs. These programs should include multiple access points

and methods of delivery, focus on reducing sexual risks, actively refer drug users to other services, focus additional efforts on preventing hepatitis C, and incorporate strong program and component evaluations.

REFERENCES

Abdala N, Stephens PC, Griffith BP, Heimer R. 1999. Survival of HIV-1 in syringes. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*. 20(1):73–80.

Abdala N, Gleghorn AA, Carney JM, Heimer R. 2001. Can HIV-1-contaminated syringes be disinfected? Implications for transmission among injection drug users. *Journal of Acquired Immune Deficiency Syndromes*. 28(5):487–494.

Abdala N, Crowe M, Tolstov Y, Heimer R. 2004. Survival of human immunodeficiency virus type 1 after rinsing injection syringes with different cleaning solutions. *Substance Use and Misuse*. 39(4):581–600.

Anthony JC, Vlahov D, Nelson KE, Cohn S, Astemborski J, Solomon L. 1991. New evidence on intravenous cocaine use and the risk of infection with human immunodeficiency virus type 1. *American Journal of Epidemiology*. 134(10):1175–1189.

Bloom D, Mahal A, O'Flaherty L. 2006. *Economics of Needle Use and Reuse*. Unpublished manuscript. Boston, MA: Department of Population and International Health, Harvard University School of Public Health.

Bluthenthal RN, Kral AH, Gee L, Erringer EA, Edlin BR. 2000. The effect of syringe exchange use on high-risk injection drug users: A cohort study. *AIDS*. 14(5):605–611.

Broadhead RS, van Hulst Y, Heckathorn DD. 1999. The impact of a needle exchange's closure. *Public Health Reports*. 114:439–447.

Bruneau J, Lamothe F, Franco E, Lachance N, Desy M, Soto J, Vincelette J. 1997. High rates of HIV infection among injection drug users participating in needle exchange programs in Montreal: Results of a cohort study. *American Journal of Epidemiology*. 146(12):994–1002.

Bruneau J, Brogly SB, Tyndall MW, Lamothe F, Franco EL. 2004. Intensity of drug injection as a determinant of sustained injection cessation among chronic drug users: The interface with social factors and service utilization. *Addiction*. 99(6):727–737.

Burris S, Strathdee S, Vernick J. 2003. Lethal injections: The law, science, and politics of syringe access for injection drug users. *University of San Francisco Law Review*. 37: 813–885.

Carlson RG, Wang J, Siegal HA, Falck RS. 1998. A preliminary evaluation of a modified needle-cleaning intervention using bleach among injection drug users. *AIDS Education and Prevention*. 10(6):523–532.

CDC (Centers for Disease Control and Prevention). 2004. *Syringe Disinfection for Injection Drug Users*. [Online]. Available: http://www.cdc.gov/idu/facts/disinfection.pdf [accessed June 29, 2006].

Chaisson RE, Osmond D, Moss AR, Feldman HW, Bernacki P. 1987. HIV, bleach, and needle sharing. *Lancet*. 1(8547):1430.

Chaisson RE, Bacchetti P, Osmond D, Brodie B, Sande MA, Moss AR. 1989. Cocaine use and HIV infection in intravenous drug users in San Francisco. *Journal of the American Medical Association*. 261(4):561–565.

Chen HT, Liao Q. 2005. A pilot study of the NGO based relational intervention model for HIV prevention among drug users in China. *AIDS Education and Prevention*. 17(6): 503–514.

Coffin P, Ahern J, Dorris S, Stevenson L, Fuller C, Vlahov D. 2002. More pharmacists in high-risk neighborhoods of New York City support selling syringes to injection drug users. *Journal of the American Pharmaceutical Association*. 42(Suppl. 2):S62–S67.

Collins C, Kohler C, DiClemente R, Wang MQ. 1999. Evaluation of the exposure effects of a theory-based street based outreach HIV intervention on African-American drug users. *Evaluation and Program Planning*. 22:279–293.

Colon HM, Sahai H, Robles RR, Matos TD. 1995. Effects of a community outreach program in HIV risk behaviors among injection drug users in San Juan, Puerto Rico: An analysis of trends. *AIDS Education and Prevention*. 7(3):195–209.

Contoreggi C, Jones S, Simpson P, Lange WR, Meyer WA 3rd. 2000. Effects of varying concentrations of bleach on in vitro HIV-1 replication and the relevance to injection drug use. *Intervirology*. 43(1):1–5.

Coutinho R. 2005 (December 20). *Needle Exchange: The Amsterdam Experience*. Presentation at the Institute of Medicine Workshop on the Prevention of HIV Among Injecting Drug Users in High-Risk Countries, Geneva, Switzerland. Institute of Medicine Committee on the Prevention of HIV Infection Among Injecting Drug Users in High-Risk Countries.

Coyle SL, Needle RH, Normand J. 1998. Outreach-based HIV prevention for injecting drug users: A review of published outcome data. *Public Health Reports*. 113 Suppl 1:19–30.

Cox GM, Lawless MC, Cassin SP, Geoghegan TW. 2000. Syringe exchanges: A public health response to problem drug use. *Irish Medical Journal*. 93(5):143–146.

Darke S. 1998. Self report among injecting drug users: A review. *Drug and Alcohol Dependence*. 51:253–263.

Deren S, Fuller C, Pouget E, Blaney S, Tortu S, Kang SY. 2003. Impact of expanding syringe access in New York on sources of syringes for injection drug users in Harlem and the Bronx, NYC, USA. *International Journal of Drug Policy*. 14:373–379.

Deren S, Cleland CM, Fuller C, Kang S-Y, Des Jarlais DC, Vlahov D. 2006. The impact of syringe deregulation on sources of syringes for injection drug users: Preliminary findings. *AIDS and Behavior*. [Online]. Epub ahead of print: April 26, 2006.

Des Jarlais DC, Hagan H, Friedman S, Friedmann P, Goldberg D, Frischer M, Green S, Tunving K, Ljungberg B, Wodak A, Ross M, Purchase D, Millson M, Myers T. 1995. Maintaining low HIV seroprevalence in populations of injecting drug users. *Journal of the American Medical Association*. 274(15):1226–1231.

Des Jarlais DC, Paone D, Milliken J, Turner CF, Miller H, Gribble J, Shi Q, Hagan H, Friedman SR. 1999. Audio-computer interviewing to measure risk behaviour for HIV among injecting drug users: A quasi-randomised trial. *Lancet*. 353(9165):1657–1661.

Des Jarlais DC, Perlis T, Friedman SR, Chapman T, Kwok J, Rockwell R, Paone D, Milliken J, Monterroso E. 2000. Behavioral risk reduction in a declining HIV epidemic: Injection drug users in New York City, 1990-1997. *American Journal of Public Health*. 90(7): 1112–1116.

Des Jarlais DC, McKnight C, Friedmann P. 2002. Legal syringe purchases by injection drug users, Brooklyn and Queens, NYC, 2000-2001. *Journal of the American Pharmaceutical Association*. 42(6)Suppl 2:S73–S76.

Des Jarlais DC, Perlis T, Arasteh K, Torian LV, Hagan H, Beatrice S, Smith L, Wethers J, Milliken J, Mildvan D, Yancovitz S, Friedman SR. 2005a. Reductions in hepatitis C virus and HIV infections among injecting drug users in New York City, 1990–2001. *AIDS*. 19 Suppl 3:S20–S25.

Des Jarlais DC, Perlis T, Arasteh K, Torian LV, Beatrice S, Milliken J, Mildvan D, Yancovitz S, Friedman SR. 2005b. HIV incidence among injection drug users in New York City, 1990 to 2002: Use of serologic test algorithm to assess expansion of HIV prevention services. *American Journal of Public Health*. 95(8):1439–1444.

Diaz T, Des Jarlais DC, Vlahov D, Perlis T, Edwards V, Friedman S, Rockwell R, Hoover D, Williams I, Monterroso E. 2001. Factors associated with prevalent hepatitis C: Differences among young adult injection drug users in lower and upper Manhattan, New York City. *American Journal of Public Health*. 91(1):23–30.

Doherty MC, Junge B, Rathouz P, Garfein RS, Riley E, Vlahov D. 2000. The effect of a needle exchange program on numbers of discarded needles: A 2-year follow-up. *American Journal of Public Health*. 90(6):936–939.

Dolan K, Kimber J, Fry C, Fitzgerald J, McDonald D, Trautmann F. 2000. Drug consumption facilities in Europe and the establishment of supervised injecting centres in Australia. *Drug and Alcohol Review*. 19:337–346.

Donoghoe MC, Stimson GV, Dolan KA. 1989. Sexual behaviour of injecting drug users and associated risks of HIV infection for non-injecting sexual partners. *AIDS Care*. 1(1): 51–58.

Druce JD, JardineD, Locarnini SA, Birch CJ. 1995. Susceptibility of HIV to inactivation by disinfectants and ultraviolet light. *Journal of Hospital Infection*. 30(3):167–180.

Empelen PV, Kok G, van Kesteren N, van den Borne B, Bos, A, Schaalma H. 2003. Effective methods to change sex-risk among drug users: A review of psychosocial interventions. *Social Science and Medicine*. 57:1593–1608.

Flynn N, Jain S, Keddie EM, Carlson JR, Jennings MB, Haverkos HW, Nassar N, Anderson R, Cohen S, Goldberg D. 1994. In vitro activity of readily available household materials against HIV-1: Is bleach enough? *Journal of Acquired Immune Deficiency Syndromes*. 7(7):747–753.

Froner GA, Rutherford GW, Rokeach M. 1987. Injection of sodium hypochlorite by intravenous drug users [letter]. *Journal of the American Medical Association*. 258(3):325.

Fuller C, Galea S, Blaney S, Ompad DC, Deren S, Des Jarlais DC, Vlahov D. 2004. Explaining the relationship between race/ethnicity and pharmacy purchased syringes among injection drug users in New York City. *Ethnicity and Disease*. 14:589–596.

Galea S, Ahern J, Fuller C, Freudenberg N, Vlahov D. 2001. Needle exchange programs and experiences of violence in an inner city neighborhood. *Journal of Acquired Immune Deficiency Syndromes*. 28(3):282–288.

Gambia Hepatitis Study Group. 1987. The Gambia Hepatitis Intervention Study. *Cancer Research*. 47:5782–5787.

Gibson DR, Brand R, Anderson K, Kahn JG, Perales D, Guydish J. 2002. Two- to sixfold decreased odds of HIV risk behavior associated with use of syringe exchange. *Journal of Acquired Immune Deficiency Syndromes*. 31(2):237–242.

Gleghorn AA, Doherty MC, Vlahov D, Celentano D, Jones T. 1994. Inadequate bleach contact times during syringe cleaning among injection drug users. *Journal of Acquired Immune Deficiency Syndromes*. 7(7):767–772.

GRADE Working Group. 2004. Grading quality of evidence and strength of recommendation. *British Medical Journal*. 328:1490–1498.

Grau LE, Arevalo S, Catchpool C, Heimer R. 2002. Expanding harm reduction services through a wound and abscess clinic. *American Journal of Public Health*. 92(12):1915–1917.

Groseclose SL, Weinstein B, Jones TS, Valleroy LA, Fehrs LJ, Kassler WJ. 1995. Impact of increased legal access to needles and syringes on practices of injecting-drug users and police officers—Connecticut, 1992-1993. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*. 10(1):82–89.

Guydish J, Clark G, Garcia D, Downing M, Case P, Sorensen JL. 1991. Evaluating needle exchange: Do distributed needles come back? *American Journal of Public Health*. 81(5): 617–619.

Hagan H, Thiede H. 2000. Changes in injection risk behavior associated with participation in the Seattle needle-exchange program. *Journal of Urban Health*. 77(3):369–382.

Hagan H, Des Jarlais DC, Purchase D, Friedman SR, Reid T, Bell TA. 1993. An interview study of participants in the Tacoma, Washington, syringe exchange. *Addiction*. 88(12): 1691–1697.

Hagan H, Des Jarlais DC, Friedman SR, Purchase D, Alter MJ. 1995. Reduced risk of hepatitis B and hepatitis C among injection drug users in the Tacoma syringe exchange program. *American Journal of Public Health*. 85(11):1531–1537.

Hagan H, McGough JP, Thiede H, Weiss NS, Hopkins S, Alexander ER. 1999. Syringe exchange and risk of infection with hepatitis B and C viruses. *American Journal of Epidemiology*. 149:203–213.

Hagan H, McGough JP, Thiede H, Hopkins SG, Weiss NS, Alexander ER. 2000. Volunteer bias in nonrandomized evaluations of the efficacy of needle-exchange programs. *Journal of Urban Health*. 77(1):103–112.

Hagan H, Thiede H, Weiss N, Hopkins S, Duchin J, Alexander ER. 2001. Sharing of drug preparation equipment as a risk factor for hepatitis C. *American Journal of Public Health*. 91(1):42–46.

Hahn JA, Page-Shafer K, Lum PJ, Bourgois P, Stein E, Evans J, Busch M, Tobler L, Phelps B, Moss AR. 2002. Hepatitis C virus seroconversion among young injection drug users: Relationships and risks. *Journal of Infectious Diseases*. 186:1558–1564.

Hammett TM, Bartlett NA, Chen Y, Ngu D, Cuong DD, Phuong NM, Tho NH, Van LK, Donghua M, Shaomi X, Chen H, Quyen HN, Broadhead RS, Des Jarlais DC. 2005. Law enforcement influences on HIV prevention for injection drug users: Observations from a cross-border project in China and Vietnam. *International Journal of Drug Policy*. 16: 235–245.

Hammett TM, Kling R, Johnston P, Liu W, Ngu D, Friedmann P, Binh KT, Dong HV, Van LK, Donghua M, Chen Y, Des Jarlais DC. 2006. HIV prevalence and HIV risk behaviors among injection drug users prior to and 24 months following implementation of cross-border interventions in Northern Vietnam and Southern China. *AIDS Education and Prevention*. 18:97–115.

Hangzo C, Chatterjee A, Sarkar S, Zomi GT, Deb BC, Abdul-Quader AS. 1997. Reaching out beyond the hills: HIV prevention among injecting drug users in Manipur, India. *Addiction*. 92(7):813–820.

Hankins C, Alary M, Parent R, Blanchette C, Claessens C; SurvUDI Working Group. 2002. Continuing HIV transmission among injection drug users in Eastern Central Canada: The SurvUDI Study, 1995 to 2000. *Journal of Acquired Immune Deficiency Syndromes*. 30(5):514–521.

Hart GJ, Carvell AL, Woodward N, Johnson AM, Williams P, Parry JV. 1989. Evaluation of needle exchange in central London: Behaviour change and anti-HIV status over one year. *AIDS*. 3(5):261–265.

Hartgers C, van Ameijden EJ, van den Hoek JA, Coutinho RA. 1992. Needle sharing and participation in the Amsterdam Syringe Exchange program among HIV-seronegative injecting drug users. *Public Health Reports*. 107(6):675–681.

Heimer R, Khoshnood K, Bigg D, Guydish J, Junge B. 1998. Syringe use and reuse: Effects of syringe exchange programs in four cities. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*. 18(Suppl 1):S37–S44.

Heinemann A, Gross U. 2001. Prevention of bloodborne virus infections among drug users in an open prison by syringe vending machines. *Sucht*. 47(1):57.

Huo D, Bailey SL, Garfein RS, Ouellet LJ. 2005. Changes in the sharing of drug injection equipment among street-recruited injection drug users in Chicago, Illinois, 1994-1996. *Substance Use and Misuse*. 40(1):63–76.

Hurley SF, Jolley DJ, Kaldor JM. 1997. Effectiveness of needle-exchange programmes for prevention of HIV infection. *Lancet.* 349(9068):1797–1800.

Jamner MS, Wolitski RJ, Corby NH. 1997. Impact of a longitudinal community HIV intervention targeting injecting drug users' stage of change for condom and bleach use. *American Journal of Health Promotion Stages of Change.* 12(1):15–24.

Jones TS, Coffin PO. 2002. Preventing blood-borne infections through pharmacy syringe sales and safe community syringe disposal. *Journal of American Pharmaceutical Association.* 42(6)Suppl 2:S6–S9.

Käll K. 2005 (December 19). *What Science Tells Us About Needle Exchange Programs.* Presentation at the Institute of Medicine Workshop on the Prevention of HIV Among Injecting Drug Users in High-Risk Countries, Geneva, Switzerland. Institute of Medicine Committee on the Prevention of HIV Infection Among Injecting Drug Users in High-Risk Countries.

Kapadia F, Vlahov D, Des Jarlais DC, Strathdee SA, Ouellet L, Kerndt P, Morse E EV, Williams I, Garfein RS; Second Collaborative Injection Drug User Study (CIDUS-II) Group. 2002. Does bleach disinfection of syringes protect against hepatitis C infection among young adult injection drug users? *Epidemiology.* 13(6):738–741.

Kaplan E, Heimer R. 1992. HIV prevalence among intravenous drug users: Model-based estimates from New Haven's legal needle exchange. *Journal of Acquired Immune Deficiency Syndromes.* 5:163–169.

Kaplan E, O'Keefe E. 1993. Let the needles do the talking! Evaluating the New Haven needle exchange. *Interfaces.* 23:7–26.

Kaplan E, Khoshnood K, Heimer R. 1994. A decline in HIV-infected needles returned to New Haven's needle exchange program: Client shift or needle exchange? *American Journal of Public Health.* 84(12):1991–1993.

Keene J, Stimson GV, Jones S, Parry-Langdon N. 1993. Evaluation of syringe-exchange for HIV prevention among injecting drug users in rural and urban areas of Wales. *Addiction.* 88(8):1063–1070.

Kerr T, Tyndall M, Li K, Montaner J, Wood E. 2005. Safer injection facility use and syringe sharing in injection drug users. *Lancet.* 366(9482):316–318.

Klee H, Faugier J, Hayes C, Morris J. 1991. The sharing of injecting equipment among drug users attending prescribing clinics and those using needle-exchanges. *British Journal of Addiction.* 86(2):217–223.

Klein S, Candelas A, Birkhead G. 2002. Mobilizing public and private partners to support New York's expanded syringe access demonstration program. *Journal of American Pharmaceutical Association.* 42(6)Suppl 2:S28–S29.

Krol A, Lindenburg K, Thijs van der Helm J, Smit C, Coutinho R, Prins M. 2006 (April 30–May 4). *Decline in Injecting Drug Use, But Not in Sexual Risk Behavior, Seen in the Amsterdam Cohort Study Among Drug Users.* 17th International Conference on the Reduction of Drug Related Harm. Abstract We_15_2. Vancouver, Canada.

Ksobiech K. 2004. Return rates for needle exchange programs: A common criticism answered. *Harm Reduction Journal.* 1(1):2.

Kumar MS, Mudaliar S, Daniels D. 1998. Community-based outreach HIV intervention for street-recruited drug users in Madras, India. *Public Health Reports.* 113 Suppl 1:58–66.

Latkin C, Sherman S, Knowlton A. 2003. HIV prevention among drug users: Outcome of a network-orientated peer outreach intervention. *Health Psychology.* 22(4):332–339.

Lewis BA, Koester SK, Bush TW. 2002. Pharmacists' attitudes and concerns regarding syringe sales to injection drug users in Denver, Colorado. *Journal of American Pharmaceutical Association.* 42(6 Suppl 2):S46–S51.

Longshore D, Bluthenthal RN, Stein MD. 2001. Needle exchange program attendance and injection risk in Providence, Rhode Island. *AIDS Education and Prevention*. 13(1): 78–90.

Lurie P, Reingold AL, Bowser B, Chen D, Foley J, Guydish J, Kahn JG, Lane S, Sorensen J. 1993. *The Public Health Impact of Needle Exchange Programs in the United States and Abroad, Volume 1*. San Francisco: University of California.

Macalino GE, Celentano DD, Latkin C, Strathdee SA, Vlahov D. 2002. Risk behaviors by audio computer-assisted self-interviews among HIV-seropositive and HIV-seronegative injection drug users. *AIDS Education and Prevention*. 14(5):367–378.

MacDonald M, Law M, Kaldor J, Hales J, Dore GJ. 2003. Effectiveness of needle and syringe programmes for preventing HIV transmission. *International Journal of Drug Policy Sterile Syringe Access for Injection Drug Users in the 21st Century: Progress and Prospects*. 14(5-6):353–357.

Mansson AS, Moestrup T, Nordenfelt E, Widell A. 2000. Continued transmission of hepatitis B and C viruses, but no transmission of human immunodeficiency virus among intravenous drug users participating in a syringe/needle exchange program. *Scandinavian Journal of Infectious Diseases*. 32(3):253–258.

Marmor M, Shore RE, Titus S, Chen X, Des Jarlais DC. 2000. Drug injection rates and needle-exchange use in New York City, 1991-1996. *Journal of Urban Health*. 77(3): 359–368.

Martin LS, McDougal JS, Loskoski SL. 1985. Disinfection and inactivation of the human T lymphotropic virus type III/Lymphadenopathy-associated virus. *Journal of Infectious Diseases*. 152(2):400–403.

Marx M, Crape B, Brookmeyer R, Junge B, Latkin C, Vlahov D, Strathdee S. 2000. Trends in crime and the introduction of a needle exchange program. *American Journal of Public Health*. 90(12):1933–1936.

McCoy CB, Rivers JE, McCoy HV, Shapshak P, Weatherby NL, Chitwood DD, Page JB, Inciardi JA, McBride DC. 1994. Compliance to bleach disinfection protocols among injecting drug users in Miami. *Journal of Acquired Immune Deficiency Syndromes*. 7(7):773–776.

Metzger DS, Koblin B, Turner C, Navaline H, Valenti F, Holte S, Gross M, Sheon A, Miller H, Cooley P, Seage GR 3rd. 2000. Randomized controlled trial of audio computer-assisted self-interviewing: Utility and acceptability in longitudinal studies. *American Journal of Epidemiology*. 152(2):99–106.

Miller CL, Tyndall M, Spittal P, Li K, Palepu A, Schechter MT. 2002. Risk-taking behaviors among injecting drug users who obtain syringes from pharmacies, fixed sites, and mobile van needle exchanges. *Journal of Urban Health*. 79(2): 257–265.

Moatti JP, Vlahov D, Feroni I, Perrin V, Obadia Y. 2001. Multiple access to sterile syringes for injection drug users: Vending machines, needle exchange programs and legal pharmacy sales in Marseille, France. *European Addiction Research*. 7(1):40–45.

Monterroso ER, Hamburger ME, Vlahov D, Des Jarlais DC, Ouellet LJ, Altice FL, Byers RH, Kerndt PR, Watters JK, Bowser BP, Fernando MD, Holmberg SD. 2000. Prevention of HIV infection in street-recruited injection drug users. The Collaborative Injection Drug User Study (CIDUS). *Journal of Acquired Immune Deficiency Syndromes*. 25(1):63–70.

Morgan DL. 1992. Intravenous injection of household bleach. *Annals of Emergency Medicine*. 21(11):1394–1395.

MSIC (Medically Supervised Injecting Centre) Evaluation Committee. 2003. *Final Report on the Evaluation of the Sydney Medically Supervised Injecting Centre*. Sydney, Australia: MSIC Evaluation Committee.

Neaigus A, Sufian M, Friedman SR, Goldsmith DS, Stepherson B, Mota P, Pascal J, Des Jarlais DC. 1990. Effects of outreach intervention on risk reduction among intravenous drug users. *AIDS Education and Prevention*. 2(4):253–271.

Needle RH, Burrows D, Friedman SR, Dorabjee J, Touze G, Badrieva L, Grund J-PC, Kumar MS, Nigro L, Manning G, Latkin C. 2005. Effectiveness of community-based outreach in preventing HIV/AIDS among injecting drug users. *International Journal of Drug Policy*. 16(Suppl 1):S45–S57.

Newmeyer JA. 1988. Why bleach? Fighting AIDS contagion among intravenous drug users: The San Francisco experience. *Journal of Psychoactive Drugs*. 20(2):159–163.

Newmeyer JA, Drew L, Miner R. 1990. HIV transmission in simulated conditions of sharing hypodermic equipment. *Journal of Acquired Immune Deficiency Syndromes*. 3:1019–1021.

NRC (National Research Council) and IOM (Institute of Medicine). 1995. *Preventing HIV Transmission: The Role of Sterile Needles and Bleach*. Washington, DC: National Academy Press.

Obadia Y, Feroni I, Perrin V, Vlahov D, Moatti JP. 1999. Syringe vending machines for injection drug users: An experiment in Marseille, France. *American Journal of Public Health*. 89(12):1852–1854.

Oelrichs RB, Shrestha IL, Anderson DA, Deacon NJ. 2000. The explosive human immunodeficiency virus type 1 epidemic among injecting drug users of Kathmandu, Nepal, is caused by a subtype C virus of restricted genetic diversity. *Journal of Virology*. 74(3): 1149–1157.

Oliver KJ, Frideman SR, Maynard H, Magnuson L, Des Jarlais DC. 1992. Impact of a needle exchange program on potentially infectious syringes in public places. *Journal of Acquired Immune Deficiency Syndromes*. 5:534–535.

Ouellet L, Huo D, Bailey SL. 2004. HIV risk practices among needle exchange users and nonusers in Chicago. *Journal of Acquired Immune Deficiency Syndromes*. 37(1):1187–1196.

Patrick DM, Strathdee SA, Archibald CP, Ofner M, Craib KJ, Cornelisse PG, Schechter MT, Rekart ML, O'Shaughnessy MV. 1997. Determinants of HIV seroconversion in injection drug users during a period of rising prevalence in Vancouver. *International Journal of STDs and AIDS*. 8(7):437–445.

Peak A, Rana S, Maharjan SH, Jolley D, Crofts N. 1995. Declining risk for HIV among injecting drug users in Kathmandu, Nepal: The impact of a harm-reduction programme. *AIDS*. 9(9):1067–1070.

Pollack HA, Khoshnood K, Blankenship KM, Altice FL. 2002. The impact of needle exchange-based health services on emergency department use. *Journal of General Internal Medicine*. 17(5):341–348.

Porter J, Metzger D, Scotti R. 2002. Bridge to services: Drug injectors' awareness and utilization of drug user treatment and social service referrals, medical care, and HIV testing provided by needle exchange programs. *Substance Use and Misuse*. 37(11):1305–1330.

Pouget ER, Deren S, Fuller C, Blaney S, McMahon J, Kang SY, Tortu S, Andia J, Des Jarlais DC, Vlahov D. 2005. Receptive syringe sharing among injection drug users in Harlem and the Bronx during the New York State Expanded Syringe Access Demonstration Program. *Journal of Acquired Immune Deficiency Syndromes*. 39:471–477.

Resnick L, Veren K, Salahudin Z, Tondreau S, Markham PD. 1986. Stability and inactivation of HTLV-III/LAV under clinical and laboratory environments. *Journal of the American Medical Association*. 255(14):1887–1891.

Rich JD, Wolf FA, Macalino G. 2002. Strategies to improve access to sterile syringes for injection drug users. *AIDS Reader*. 12:527–535.

Rich JD, McKenzie M, Macalino GE, Taylor LE, Sanford-Colby S, Wolf F, McNamara S, Mehrotra M, Stein MD. 2004. A syringe prescription program to prevent infectious disease and improve health of injection drug users. *Journal of Urban Health*. 81(1): 122–134.

Rietmeijer CA, Kane MS, Simons PZ, Corby NH, et al. 1996. Increasing the use of bleach and condoms among injecting drug users in Denver: Outcomes of a targeted, community-level HIV prevention program. *AIDS*. 10(3):291–298.

Riley ED, Robnett TJ, Vlahov D, Vertefeuille J, Strathdee SA, Chaisson RE. 2000. Computer-assisted self-interviewing for HIV and tuberculosis risk factors among injection drug users participating in a needle exchange program. *American Journal of Epidemiology*. 151(11):S55-S55.

Riley ED, Wu AW, Junge B, Marx M, Strathdee SA, Vlahov D. 2002. Health services utilization by injection drug users participating in a needle exchange program. *American Journal of Drug and Alcohol Abuse*. 28(3):497–511.

Rowden DW, Dorsey PE, Bullman S, Lestina RP, Han C, Herrell JM. 1999. HIV outreach for hard-to-reach populations: A cross-site perspective. *Evaluation and Program Planning*. 22(3):251–258.

Safaeian M, Brookmeyer R, Vlahov D, Latkin C, Marx M, Strathdee SA. 2002. Validity of self-reported needle exchange attendance among injection drug users: Implications for program evaluation. *American Journal of Epidemiology*. 155(2):169–175.

Sarkar K, Mitra S, Bal B, Chakraborty S, Bhattacharya SK. 2003. Rapid spread of hepatitis C and needle exchange programme in Kolkata, India. *Lancet*. 361(9365):1301–1302.

Schechter MT, Strathdee SA, Cornelisse PG, Currie S, Patrick DM, Rekart ML, O'Shaughnessy MV. 1999. Do needle exchange programmes increase the spread of HIV among injection drug users?: An investigation of the Vancouver outbreak. *AIDS*. 13(6):F45–F51.

Schoenbaum EE, Hartel DM, Gourevitch MN. 1996. Needle exchange use among a cohort of injecting drug users. *AIDS*. 10(14):1729–1734.

Semaan S, Des Jarlais DC, Sogolow E, Johnson WD, Hedges LV, Ramirez G, Flores SA, Norman L , Sweat MD, Needle R. 2002. A meta-analysis of the effect of HIV prevention interventions on the sex behaviors of drug users in the United States. *Journal of Acquired Immune Deficiency Syndromes*. 30(Suppl 1):S73–S93.

Shapshak P, McCoy CB, Shah SM, Page JB, Rivers JE, Weatherby NL, Chitwood DD, Mash DC. 1994. Preliminary laboratory studies of inactivation of HIV-1 in needles and syringes containing infected blood using undiluted household bleach. *Journal of Acquired Immune Deficiency Syndromes*. 7(7):754–759.

Singer M, Himmelgreen D, Weeks MR, Radda KE, Martinez R. 1997. Changing the environment of AIDS risk: Findings on syringe exchange and pharmacy sales of syringes in Hartford, CT. *Medical Anthropology*. 18(1):107–130.

Spire B, Barre-Sinoussi F, Montagnier L, Chermann JC. 1984. Inactivation of lymphadenopathy associated virus by chemical disinfectants. *Lancet*. 2(8408): 899–901.

Stancliff S, Salomon N, Perlman DC, Russell PC. 2000. Provision of influenza and pneumococcal vaccines to injection drug users at a syringe exchange. *Journal of Substance Abuse Treatment*. 18(3):263–265.

Stark K, Leicht A, Muller R. 1994. Characteristics of users of syringe vending machines in Berlin. *Sozial und Präventivmedizin*. 39(4):209–216.

Strathdee SA, Patrick DM, Currie SL, Cornelisse PG, Rekart ML, Montaner JS, Schechter MT, O'Shaughnessy MV. 1997. Needle exchange is not enough: Lessons from the Vancouver injecting drug use study. *AIDS*. 11(8):F59–65.

Strathdee SA, Celentano DD, Shah N, Lyles C, Stambolis VA, Macalino G, Nelson K, Vlahov D. 1999. Needle-exchange attendance and health care utilization promote entry into detoxification. *Journal of Urban Health*. 76(4):448–460.

Taussig J, Junge B, Burris S, Jones TS, Sterk CE. 2002. Individual and structural influences shaping pharmacists' decisions to sell syringes to injection drug users in Atlanta, Georgia. *Journal of the American Pharmaceutical Association*. 42(6 Suppl 2):S40–S45.

Taylor A, Goldberg D, Hutchinson S, Cameron S, Gore SM, McMenamin J, Green S, Pithie A, Fox R. 2000. Prevalence of hepatitis C virus infection among injecting drug users in Glasgow 1990-1996: Are current harm reduction strategies working? *Journal of Infectious Diseases*. 40(2):176–183.

Thorpe L, Ouellet L, Hershow R, Bailey S, Williams I, Williamson J, Monterroso E, Garfein R. 2002. Risk of hepatitis C virus infection among young adult injection drug users who share injection equipment. *American Journal of Epidemiology*. 155(7):645–653.

Titus S, Marmor M, Des Jarlais D, Kim M, Wolfe H, Beatrice S. 1994. Bleach use and HIV seroconversion among New York City injection drug users. *Journal of Acquired Immune Deficiency Syndromes*. 7(7):700–704.

Tyndall M, Kerr T, Zhang R, King E, Montaner J, Wood E. 2006. Attendance, drug use patterns, and referrals made from North America's first supervised injection facility. *Drug and Alcohol Dependence*. 83(2):193–198.

UN Nepal Information Platform. 2005. *HIV/AIDS Epidemiological Situation*. [Online]. Available: http://www.un.org.np/hivaids.php#nat [accessed June 23, 2006].

van Ameijden EJ, Coutinho RA. 1998. Maximum impact of HIV prevention measures targeted at injecting drug users. *AIDS*. 12(6):625–633.

van Ameijden EJ, Coutinho RA. 2001. Large decline in injecting drug use in Amsterdam, 1986-1998: Explanatory mechanisms and determinants of injecting transitions. *Journal of Epidemiology and Community Health*. 55(5):356–363.

van Ameijden EJ, van den Hoek JA, van Haastrecht HJ, Coutinho RA. 1992. The harm reduction approach and risk factors for human immunodeficiency virus (HIV) seroconversion in injecting drug users, Amsterdam. *American Journal of Epidemiology*. 136(2):236–243.

van Ameijden EJ, van den Hoek AR, Coutinho RA. 1994. Injecting risk behavior among drug users in Amsterdam, 1986 to 1992, and its relationship to AIDS prevention programs. *American Journal of Public Health*. 84(2):275–281.

Van Bueren J, Simpson RA, Salman H, Farrelly HD, Cookson BD. 1995. Inactivation of HIV-1 by chemical disinfectants: Sodium hypochlorite. *Epidemiology and Infection*. 115: 567–579.

van den Hoek JA, van Haastrecht HJ, Coutinho RA. 1989. Risk reduction among intravenous drug users in Amsterdam under the influence of AIDS. *American Journal of Public Health*. 79(10):1355–1357.

Vazirian M, Nassirimanesh B, Zamani S, Ono-Kihara M, Kihara M, Ravari SM, Gouya MM. 2005. Needle and syringe sharing practices of injecting drug users participating in an outreach HIV prevention program in Tehran, Iran: A cross-sectional study. *Harm Reduction Journal*. 2:19.

Vertefeuille J, Marx MA, Tun W, Huettner S, Strathdee SA, Vlahov D. 2000. Decline in self-reported high-risk injection-related behaviors among HIV-seropositive participants in the Baltimore needle exchange program. *AIDS and Behavior*. 4(4):381–388.

Vickerman P, Hickman M, Rhodes T, Watts C. 2006. Model projections on the required coverage of syringe distribution to prevent HIV epidemics among injecting drug users. *Journal of Acquired Immune Deficiency Syndromes*. 42(3):355–361.

Vlahov D. 2000. The role of epidemiology in needle exchange programs comment on A R Moss. *American Journal of Public Health*. 90(9):1390–1392.

Vlahov D, Munoz A, Celentano DD, Cohn S, Anthony JC, Chilcoat H, Nelson KE. 1991. HIV seroconversion and disinfection of injection equipment among intravenous drug users, Baltimore, Maryland. *Epidemiology*. 2(6):444–446.

Vlahov D, Astemborski J, Solomon L, Nelson KE. 1994. Field effectiveness of needle disinfection among injecting drug users. *Journal of Acquired Immune Deficiency Syndromes*. 7(7):760–766.

Vlahov D, Junge B, Brookmeyer R, Cohn S, Riley E, Armenian H, Beilenson P. 1997. Reductions in high-risk drug use behaviors among participants in the Baltimore needle exchange program. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*. 16(5):400–406.

Watters JK, Estilo MJ, Clark GL, Lorvick J. 1994. Syringe and needle exchange as HIV/AIDS prevention for injection drug users. *Journal of the American Medical Association*. 271(2): 115–120.

Weber DJ, Barbee SL, Sobsey MD, Rutala WA. 1999. The effect of blood on the antiviral activity of sodium hypochlorite, a phenolic, and a quaternary ammonium compound. *Infection Control and Hospital Epidemiology*. 20(12):821–827.

Wiebel WW, Jimenez A, Johnson W, Ouellet L, Jovanovic B, Lampinen T, Murray J, O'Brien MU. 1996. Risk behavior and HIV seroincidence among out-of-treatment injection drug users: A four-year prospective study. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*. 12(3):282–289.

Wood E, Tyndall MW, Spittal PM, Li K, Hogg RS, Montaner JS, O'Shaughnessy MV, Schechter MT. 2002. Factors associated with persistent high-risk syringe sharing in the presence of an established needle exchange programme. *AIDS*. 16(6):941–943.

Wood E, Kerr T, Spittal PM, Small W, Tyndall MW, O'Shaughnessy MV, Schechter MT. 2003. An external evaluation of a peer-run "unsanctioned" syringe exchange program. *Journal of Urban Health*. 80(3):455–464.

Wood E, Kerr T, Lloyd-Smith E, Buchner C, Marsh D, Montaner J, Tyndall M. 2004a. Methodology for evaluating Insite: Canada's first medically supervised safer injection facility for injection drug users. *Harm Reduction Journal*. 1:9.

Wood E, Kerr T, Small W, Li K, Marsh D, Montaner J, Tyndall M. 2004b. Changes in public order after the opening of a medically supervised safer injecting facility for illicit injection drug users. *Canadian Medical Association Journal*. 171(7):731–734.

Wood E, Tyndall M, Lai C, Montaner J, Kerr T. 2006a. Impact of a medically supervised safer injecting facility on drug dealing and other drug-related crimes. *Substance Abuse Treatment, Prevention, and Policy*. 1:13.

Wood E, Tyndall M, Zhang R, Stoltz J, Lai C, Montaner J, Kerr T. 2006b. Attendance at supervised injecting facilities and use of detoxification services. *New England Journal of Medicine*. 354(23):2512–2514.

4

Taking Action

The threat of an impending HIV epidemic in many countries now facing the contributing injection drug use epidemic is clear. The need to implement effective and cost-effective programs is also clear. The challenges for policymakers are to, informed by evidence, choose options for action, and tailor these interventions to a country's unique economic, political, cultural, legal, and public health context.

Chapters 2 and 3 presented evidence on the effectiveness of HIV prevention interventions for injecting drug users, to inform such policymaking. This chapter summarizes the Committee's findings regarding the effectiveness of those interventions, knowledge gaps, and future research needs. The chapter also presents considerations for policymakers in high-risk countries in shaping their HIV prevention programs for IDUs. Based on these considerations, the Committee offers recommendations for countries implementing such programs.

SUMMARY OF THE EVIDENCE

Eastern Europe, the Commonwealth of Independent States, and significant parts of Asia are experiencing explosive growth in new HIV infections, driven largely by injecting drug use (UNAIDS, 2006). While the primary route of transmission in most of these areas is sharing of contaminated injecting equipment, sexual and perinatal transmission among IDUs and their partners also plays an important and growing role. In many highly affected countries, rapid growth in the number of IDUs infected with HIV

has already created a public health crisis. Countries where the level of HIV infection is still relatively low have the chance—if they act now—to slow the spread of HIV.

A variety of HIV prevention programs targeting IDUs have been shown to be effective in reducing HIV-related risks.[1] For injecting opioid users seeking treatment, opioid agonist maintenance treatment is the only consistently effective treatment for opioid dependence. Studies show that methadone and buprenorphine reduce illicit opioid use, injection-related HIV risk behavior, and risk of HIV seroconversion among people with opioid dependence. Opioid antagonist medication is another pharmacological treatment option for opioid-dependent individuals who will not accept or cannot gain access to opioid agonist maintenance therapy. Despite strong pharmacological evidence and theoretical potential for naltrexone, evidence regarding its efficacy in controlled clinical trials is inconclusive. Naltrexone is likely to be most successful for patients whose adherence to medication and retention in treatment can be closely monitored and facilitated. Psychosocial interventions alone have not been shown to be consistently effective in treating opioid dependence.

For injecting non-opioid users seeking treatment, no pharmacotherapies have been found to be consistently efficacious in treating stimulant dependence. Contingency management, a behavioral intervention, is an efficacious treatment for stimulant dependence, but additional research is needed on the feasibility of its application outside of research settings. There is modest evidence of efficacy of several other behavioral or psychotherapeutic approaches in addressing stimulant abuse, including individual drug counseling and intensive group drug counseling, cognitive behavioral therapy, and community reinforcement combined with contingency management. While there is weak evidence regarding the effectiveness of therapeutic communities, drug anonymous groups, and abstinence-based outpatient treatments, these are important treatment options for opioid-dependent individuals who will not accept or cannot gain access to opioid agonist maintenance treatment, or for individuals dependent on other classes of drugs. Those seeking effective interventions for non-opioid users should consider these behavioral or psychosocial interventions, but funders and policymakers are urged to collect rigorous evaluation data if they are selected.

For injecting drug users who cannot gain access to treatment or are not ready to consider it, multi-component HIV prevention programs that include sterile needle and syringe access reduce drug-related HIV risk behav-

[1]Refer to Chapters 2 and 3 for a detailed and properly referenced discussion of the evidence related to HIV prevention for IDUs.

ior, including self-reported sharing of needles and syringes, unsafe injecting and disposal practices, and frequency of injection. Sterile needle and syringe access may include needle and syringe exchange (NSE) or the legal, accessible, and economical sale of needles and syringes through pharmacies, voucher schemes, and physician prescription programs. Other components of multi-component HIV prevention programs may include outreach, education in risk reduction, HIV voluntary counseling and testing, condom distribution, distribution of bleach and education on needle disinfection, and referrals to substance abuse treatment and other health and social services. If sterile needle and syringe access is not available, IDUs can prevent HIV transmission if they properly use bleach to disinfect injecting equipment. Finally, outreach and education reduces self-reported drug-related risk behavior, and is an important and effective strategy for encouraging behavioral change, providing education on preventing HIV transmission, and referring IDUs to other health and social services.

Yet knowledge gaps remain regarding the effectiveness of some HIV prevention programs among IDUs. More research is needed to identify the additional benefits and cost-effectiveness of adding psychosocial interventions to opioid agonist maintenance treatment for opioid-dependent people in high-risk countries, and to determine the relative effectiveness of those interventions in particular cultural contexts and patient subgroups. Research is also needed on the relative effectiveness of various psychosocial interventions in treating opioid dependence in situations where opioid agonist maintenance therapy is not available or accessible. Finally, research is needed on the effectiveness of naltrexone for different patient populations and in different settings.

For non-opioid dependence, research is needed regarding effective pharmacotherapies for stimulant abuse, particularly amphetamine-type stimulants, which have emerged as a major problem in many parts of the world. In addition, there is a need to develop cost-effective and feasible alternatives to voucher-based contingency management approaches for treating stimulant dependence.

Related to sterile needle and syringe access, several areas deserve future research. For example, information on unintended consequences from needle and syringe exchange—such as the possibility of recruitment of new drug users and expansion of drug networks—is scarce. Although the few studies that have examined unintended consequences have not found them, future evaluations should look specifically for unintended outcomes, and—if found—develop strategies for addressing them.

In addition, while laboratory studies have shown that undiluted bleach is an effective disinfection agent, field studies show that, in practice, drug users do not correctly follow disinfection procedures, and that they fail to effectively disinfect syringes. More research is therefore needed on alterna-

tive bleach disinfection techniques that are both simple and acceptable, and on the best methods to educate IDUs on those techniques. The Committee is also aware that in some countries, bleach is not available or acceptable for use. While alternative disinfectants (such as water, alcohol, hydrogen peroxide, and detergent) have been examined in laboratory settings, the Committee did not identify any studies of the effectiveness of those options in field settings, and calls for more research in this area.

Furthermore, in light of persistently high incidence of hepatitis C virus (HCV) among needle and syringe exchange participants, more research is also needed on the impact of NSE and related prevention services on the incidence of HCV among IDUs. And while multi-component prevention programs that include needle and syringe exchange have been shown to reduce drug-related HIV risks, questions remain about the specific contribution of individual elements to reductions in risk behavior and HIV incidence. Elements of these multi-component prevention programs can be resource intensive. Further research is needed to identify the most effective and cost-effective combination of programs that are feasible to implement in high-risk countries.

As noted, we would not expect interventions that target drug-related risk behavior—such as sterile needle and syringe access and pharmacotherapy for opioid addiction—to decrease sex-related HIV risk behavior, unless they are combined with additional risk reduction efforts targeting sexual behavior. Because of the strong correlation between drug use and high-risk sexual behavior, prevention programs and evaluations should devote more attention to reducing sexual risk behavior. More research is needed to identify the most effective sexual risk reduction strategies for IDUs, and on how to successfully integrate these strategies into existing programs, such as drug dependence treatment, multi-component programs that include sterile needle and syringe access, and outreach and education.

While such knowledge gaps require further research, they should not deter developing and transitional countries from implementing HIV prevention programs, particularly those with strong evidence of effectiveness. Failing to act will lead to further spread of HIV—not only among IDUs but also in the general population through sexual and perinatal transmission.

CONSIDERATIONS FOR POLICYMAKERS

The design of approaches to control HIV epidemics among injecting drug users depends on many factors. Scientific evidence should provide the foundation for the policymaking process. However, each country and community will also consider its own economic, cultural, legal, religious, and ethical climate. The choice of programmatic strategy must factor in the local context, and local programs must be tailored to fit that context.

Economics in resource-constrained countries is a key contextual factor that can influence the choice of programs and the strategy and pace with which they are implemented. The state of the medical and public health infrastructure may also impose practical constraints on the ability to implement programs in the short-term. Policymakers must also consider the balance between criminal justice and disease prevention. The nature, extent, strengths, and infrastructure of any broader population-based efforts to intervene in drug use and HIV epidemics in general can form the basis for efforts focusing specifically on preventing HIV among IDUs. Rather than offering a formulaic approach to step-by-step implementation, the Committee provides considerations for program building and decisionmaking based on national context. Whatever criteria policymakers use to decide which programs to implement and how, they must make provisions to learn from incremental implementation—especially to address the information gaps identified in this report.

Economic Trade-Offs

Many high-risk countries face severe resource constraints. In these circumstances, HIV prevention programs for IDUs will run up against competing demands from other compelling interventions, both within the health sector and outside it. External donor funds can help ameliorate these constraints, but such resources may not be sufficient for large-scale program implementation.

Under such circumstances, financial decisionmakers may need to understand the economic advantages of pursuing HIV interventions among IDUs. Cost-effectiveness analyses (CEA) and cost-benefit analyses are standard methods used by economists to assess the potential gains from specific health and other interventions. CEA assesses the cost of achieving a one-unit gain of some outcome, such as an HIV case prevented or a death averted. Because the outcome measure is usually an indicator of health, this method is probably most useful for comparing health interventions, and therefore in allocating budgets of the Ministry of Health or donor funds allocated to health. Cost-benefit analysis is better equipped to make comparisons across various sectors, as outcomes are also evaluated in terms of money.

The bulk of existing research on the cost-effectiveness of HIV prevention programs for IDUs comes primarily from the United States and other relatively resource-rich countries. Models and empirical data from these countries indicate that methadone maintenance treatment is associated with reductions in expenditures for injection-related events such as comorbidity, crime, and transmission of HIV infection to others (Gerstein et al., 1997; Pollack and Heimer, 2004). Available literature suggests that methadone

maintenance treatment (MMT) yields monetary benefits that are several times the costs of the intervention, particularly if accompanied by incentives for drug users (Gerstein et al., 1994; Doran et al., 2003; Hartz et al., 1999). Another study—an analysis based on a randomized controlled trial—suggests that buprenorphine and methadone are equally cost-effective in the treatment of opioid dependence (Doran et al., 2003). Some mathematical models also suggest that programs that include needle and syringe exchange are cost-effective in controlling HIV transmission (Laufer, 2001; Cabases and Sanchez, 2003).

While evidence shows that both NSE and MMT are quite cost-effective in resource-rich countries, these studies are not themselves strong evidence for cost-effectiveness in high-risk countries, which are often resource-constrained. Simulation models can provide a useful platform for examining potential cost-effectiveness in populations with characteristics different from those on which existing studies are based. Thus, while developing countries can anticipate overall savings from combating HIV among IDUs, both program costs and the magnitude of the savings will vary by country, establishing the question of cost-effectiveness as an important research topic.

Cost-effectiveness can also guide implementation for countries that cannot afford a comprehensive and generally available approach—or do not have enough trained workers to implement it. These countries may find that a less efficacious yet more cost-effective program works best. For example, although research suggests that agonist maintenance therapy can be more effective if provided with psychosocial services, some countries may not be able to afford to offer counseling with such therapy, or may not have enough trained counselors. Those countries may decide initially to make agonist treatment alone widely available, to maximize the overall benefit. Other countries may choose to place initial emphasis on training medical personnel. Rigorous approaches to documenting the cost-effectiveness of different approaches, with attention to unique settings—such as the impact of large-scale programs with limited services versus smaller, more comprehensive programs, or compared with training for health counselors—are critical.

Infrastructure Needs

As discussed in Chapter 1, for effective HIV prevention efforts to exert a public health impact, they must be scaled up to provide adequate coverage of the target populations. Scaling up prevention programs, particularly opioid agonist maintenance treatment, imposes certain infrastructure requirements. These include the availability of a sufficient pool of trained treatment providers, pharmacists, outreach workers, drug and alcohol counselors, infectious disease specialists, and other professionals to carry out the

chosen programs, as well as the physical infrastructure, commodities, and funding to enable them to do so. In some places, broad scale-up of interventions will require a parallel scale-up of training and accreditation programs for health care workers. Similarly, for pharmacotherapy programs for opioid dependence, clinical guidelines (regarding patient eligibility criteria, dosage levels, and contraindications with other drugs, for example) may need to be adopted or enhanced. Information systems may also be needed to track and ensure consistent supply of commodities such as medications and needles (WHO et al., 2004; IOM, 2005).

Some high-risk countries may have limited public health, drug treatment, and overall medical infrastructure and operating capacity. These countries will have to make pragmatic decisions regarding which approaches they can pursue. Some scientifically sound and ethically acceptable approaches may not be immediately feasible in particular locations because facilities, supplies, or human capacity are inadequate. Programs with strong evidence of effectiveness may be less effective when scaled up if enough human and technical capacity is not available. Some communities may therefore have to choose between covering relatively few people with programs likely to have beneficial effects, and reaching a large number of those in need with potentially less effective programs.

The recent scale-up of antiretroviral treatment of HIV/AIDS in developing countries has highlighted some of the infrastructural challenges that may occur when expanding HIV prevention programs for IDUs (IOM, 2005). Trained physicians can provide only a small fraction of the care for HIV/AIDS, and this shortage of human resources will only worsen in many countries over the short term (IOM, 2005). Both HIV care and the care of IDUs will require a steady influx of trained professionals.

As with the scale-up of antiretroviral treatment, injecting drug users in need of care may live in densely populated urban settings, or in more disbursed rural communities with less access to services. Some policymakers consider geographic disparity in access to care unacceptable, and have quickly established widely dispersed programs (IOM, 2005). This strategy, of course, creates its own challenges, in that broadly distributed but ineffectively implemented programs may reduce the overall public health impact.

Some needs for managing HIV prevention and care in high-prevalence countries and for addressing the health needs of injecting drug users are so intertwined that close integration of programs may be advantageous by allowing the efficient sharing of physical facilities, supply chains, administrative systems, treatment providers, counselors, and other types of personnel. Efforts to combat HIV and tuberculosis have driven the development of innovative programs for ensuring that patients receive their daily dose of medication. Research also shows that providing directly administered antiretroviral therapy (DAART) at methadone clinics or as part of a com-

munity-based delivery program can lead to substantial clinical benefits for IDUs (Lucas et al., 2006). Community-based partners that support directly observed antiretroviral therapy have improved compliance in some places (Farmer et al., 2001). The global response to HIV/AIDS is also showing that reliable systems for ensuring an unbroken supply line for antiretroviral drugs are critical. The care of injecting drug users in hard-to-reach areas may benefit from some of the systems for providing outreach and acquiring and transporting commodities created for the global scale-up of HIV/AIDS.

Public Perceptions

Public perception also helps shape the choice of strategies to prevent HIV transmission and reduce illicit drug use. Some view public health interventions that provide access to sterile injecting equipment or opioid agonist treatment negatively because these interventions aim to reduce the harms related to drug use rather than prevent drug use itself (NRC and IOM, 1995; Gostin, 1991). These groups may see such harm reduction efforts as condoning rather than condemning illegal drug use. Local communities may also object to programs that include needle and syringe exchange and opioid agonist maintenance treatment because they fear that these programs will attract drug users who may commit crimes and discard needles and other drug paraphernalia in their neighborhoods (NRC and IOM, 1995). Public attitudes have affected the number and location of clinics providing opioid agonist treatment, as efforts to open such clinics sometimes elicit intense local opposition (IOM, 1995).

Stigma and discrimination can also affect whether drug users seek HIV prevention services. Public attitudes toward drug dependence are overwhelmingly negative (NRC and IOM, 1995). Medical professionals sometimes share these attitudes, and may be antagonistic to treatment. These attitudes of health care professionals can discourage IDUs from seeking treatment (Ritson, 1999), as can negative attitudes of pharmacists toward IDUs seeking to purchase clean injecting equipment (Taussig et al., 2002). Furthermore, drug treatment professionals are often divided about providing opioid agonist maintenance treatment, with some viewing it as conflicting with abstinence-based treatment (IOM, 1995).

Some national policies reflect these concerns (see the case studies in Appendix C) (NRC and IOM, 1995; Burris et al., 2003). For example, in Russia, methadone and other opioid agonist treatment programs are illegal because of the widespread view that these programs condone addiction (Personal communication, V.N. Krasnov, Russian Society of Psychiatrists, June 16, 2006). The U.S. Congress, reflecting similar concerns, banned federal funding for needle and syringe programs in 1988—and this ban remains in effect. Nonetheless, some U.S. cities allow NSE under exceptions

for public health emergencies and through other legal actions, but these programs are often funded by private donors and nongovernmental organizations, and less often by states (Burris et al., 2003).

Gostin (1991) illustrates the inherent tension—in this case in the United States but which may also occur in other countries—surrounding certain interventions: "Needle exchange programs cannot proceed without the cooperation of the very groups that traditionally oppose them-law enforcers and community leaders. The conflict between public health and criminal justice is illustrated by the dilemmas inherent in needle exchange: public health officials in some of the highest seroprevalence cities cannot establish exchange programs without first obtaining authorization from the state under needle prescription laws; the police must agree not to arrest, and the district attorney not to prosecute, people using drug paraphernalia distributed under the public health program; and community leaders must agree to the location of needle distribution centers which, if they are to be effective, need to be situated in poor urban areas." (p. 297)

Several studies suggest that the involvement and education of key stakeholders, such as community members, government agencies, nongovernmental groups, public health officials, and law enforcement are critical to the success of HIV prevention programs for IDUs. For example, a study of needle and syringe exchange in Northern Thailand found that the success of the program depended on cooperation of key parties in the community (Gray, 1995, 1998). This study recommended that mechanisms to ensure cooperation, education and training, and evaluation coincide with the introduction of needle-exchange programs (Gray, 1995). Similarly, before launching a pilot needle and syringe exchange in Vietnam, staff members conducted workshops to help build community awareness and acceptance of the program (Quan et al., 1998). Such communication often reveals that disagreements over priorities and strategies often stem from a lack of information on the focus, methods, and evidence base of the competing factions.

The Committee recommends that public health and criminal justice officials, key community leaders (religious, educational), and community members work together at international, national, regional, and local levels to develop interventions that balance their respective missions in fighting both HIV/AIDS and drug epidemics.

Sustainability and Evaluation

Concerted national efforts to limit the transmission of HIV among IDUs must begin now. Nations must approach these efforts with both immediacy, to break the cycle of HIV transmission, but also with a longer-term view, to sustain progress.

Although reviewing the evidence on primary programs for preventing

drug use was beyond the scope of its charge, the Committee believes that programs to prevent the initiation of injecting drug use—and drug use in general—can and should be part of a comprehensive, sustained approach to preventing HIV transmission among IDUs. Broader population-based efforts at HIV awareness and prevention can provide a foundation for sustaining such efforts for IDUs.

Similarly, investments in the infrastructure to deliver clinical and supportive services to the general population will be needed and will have benefits beyond the IDU population. Maintaining infrastructure and sustaining funding is central to ensuring continuous services. Programs that do not have sustainable funding are at risk of interruption. Service interruptions could have serious implications for individuals receiving medication for opioid dependence and other IDUs receiving treatment or preventive services.

As part of a sustained effort, the Committee repeats its recommendation that such approaches be monitored and evaluated, and modified based on such evaluations. Scale-up of prevention efforts should include staggered program designs or other approaches that permit the evaluation of effectiveness, alongside more rigorous efforts to experiment with different implementation choices to see which ones work best.

RECOMMENDATIONS

In making decisions regarding implementation, policymakers and other stakeholders should consider several recommendations:

Recommendation 4-1: Because a variety of interventions have been shown to be effective, high-risk countries should act now to prevent the growing problem of HIV among IDUs, their partners, and children.

Recommendation 4-2: To increase their acceptability and likelihood of success, HIV prevention interventions for IDUs should be:

- **Tailored to local circumstances and implemented in a culturally appropriate manner;**
- **Coupled with cost-effectiveness evaluations to improve resource-allocation decisions;**
- **Scaled-up to provide adequate coverage of the interventions to the target populations in order for programs to have a public health impact;**
- **Integrated with strategies to combat stigma and discrimination among drug users and HIV-infected people;**

- **Coordinated among national, regional, and local public health, criminal justice, and community leaders to develop a framework for interventions that balance their respective missions;**
- **Complementary to broader interventions in drug use and HIV, including primary prevention;**
- **Built upon plans for fiscal and infrastructure sustainability;**
- **Coupled with monitoring and evaluation.**

CONCLUSION

Nations where the HIV pandemic is newly emerging can and should take effective action now to stem the tide of this tragic and preventable illness. In countries where injecting drug use is the primary source of HIV infection, national programs must address the challenges of both drug use and HIV. The Committee has reviewed the evidence regarding interventions for injecting drug use and HIV among IDUs, and hopes it has provided policymakers a knowledge base regarding what works. The Committee recognizes though that each country will pursue a different combination of interventions, reflecting its economic circumstances and legal, ethical, and cultural traditions. However, these policy decisions should not be based on erroneous understanding if scientific truth is available. The Committee believes that the evidence-based conclusions and recommendations in this report can provide an important foundation for governments and communities engaging in economic, legal, and ethical debates about these issues.

Evidence on effective interventions provides a solid basis for action now. The experiences of other nations with extensive HIV epidemics underscore the urgent need for an immediate response. As policy unfolds into programmatic action, nations should also evaluate their implementation, to inform the next generation of responses to drug dependence and HIV.

REFERENCES

Burris S, Strathdee S, Vernick J. 2003. Lethal injections: The law, science, and politics of syringe access for injection drug users. *University of San Francisco Law Review*. 37: 813–885.

Cabases J, Sanchez E. 2003. Costs and effectiveness of a syringe distribution and needle exchange program for HIV prevention in a regional setting. *The European Journal of Health Economics*. 4(3):203–208.

Doran C, Shanahan M, Mattick R, Ali R, White J, Bell J. 2003. Buprenorphine versus methadone maintenance: A cost-effectiveness analysis. *Drug and Alcohol Dependence*. 71: 295–302.

Farmer P, Leandre F, Mukherjee J, Gupta R, Tarter L, Kim JY. 2001. Community-based treatment of advanced HIV disease: Introducing DOT-HAART (directly observed therapy with highly active antiretroviral therapy). *Bulletin of the World Health Organization*. 79(12):1145–1151.

Gerstein DR, Johnson RA, Harwood HJ, Fountain D, Suter N, Malloy K. 1994. *Evaluating Recovery Services: The California Drug and Alcohol Treatment Assessment (CALDATA)*. Fairfax, VA: Lewin-VHI and National Opinion Research Center at the University of Chicago.

Gerstein DR, Johnson RA, Larison CL. 1997. *Alcohol and Other Drug Treatment for Parents and Welfare Recipients: Outcomes, Costs, and Benefits*. Washington, DC: U.S. Department of Health and Human Services.

Gostin L. 1991. An alternative public health vision for a national drug strategy: "Treatment works." *Houston Law Review*. 28(1):285–308.

Gray J. 1995. Operating needle exchange programmes in the hills of Thailand. *AIDS Care*. 7(4):489–499.

Gray J. 1998. Harm reduction in the hills of northern Thailand. *Substance Use and Misuse*. 33(5):1075–1091.

Hartz D, Meek P, Piotrowski N, Tusel D, Henke C, Delucchi, Sees K, Hall S. 1999. A cost-effectiveness and cost-benefit analysis of contingency contracting-enhanced methadone detoxification treatment. *American Journal of Drug and Alcohol Abuse*. 25(2):207–218.

IOM (Institute of Medicine). 1995. *Federal Regulation of Methadone Treatment*. Washington, DC: National Academy Press.

IOM. 2005. *Scaling Up Treatment for the Global AIDS Pandemic: Challenges and Opportunities*. Washington, DC: The National Academies Press.

Laufer FN. 2001. Cost-effectiveness of syringe exchange as an HIV prevention strategy. *Journal of Acquired Immune Deficiency Syndromes*. 28(3):273–278.

Lucas GM, Mullen BA, Weidle PJ, Hader S, McCaul ME, Moore RD. 2006. Directly administered antiretroviral therapy in methadone clinics is associated with improved HIV treatment outcomes, compared with outcomes among concurrent comparison groups. *Clinical Infectious Diseases*. 42:1628–1635.

NRC (National Research Council) and IOM (Institute of Medicine). 1995. *Preventing HIV Transmission: The Role of Sterile Needles and Bleach*. Washington, DC: National Academy Press.

Pollack H, Heimer R. 2004. Impact and cost-effectiveness of methadone maintenance programs for HIV and hepatitis C prevention. In: Jager J, Limburg W, Kretzschmar M, Postma M, Wiessing L, eds. *Hepatitis C And Injecting Drug Use: Impact, Costs, and Policy Options*. Lisbon, Portugal: European Monitoring Centre for Drugs and Drug Addiction. 7:345–371.

Quan VM, Chung A, Abdul-Quader AS. 1998. The feasibility of a syringe-needle exchange program in Vietnam. *Substance Use and Misuse*. 33(5):1055–1067.

Ritson EB. 1999. Alcohol, drugs and stigma. *International Journal of Clinical Practice*. 53:549–551.

State Welfare Organization. 2000. Drug abuse prevention in youth needs a national movement. Tehran, Iran: State Welfare Organization (unofficial translation).

Taussig J, Junge B, Burris S, Jones TS, Sterk CE. 2002. Individual and structural influences shaping pharmacists' decisions to sell syringes to injection drug users in Atlanta, Georgia. *Journal of the American Pharmaceutical Association*. 42(6)Suppl 2:S40–S45.

WHO (World Health Organization), United Nations Office on Drugs and Crime, Joint United Nations Programme on HIV/AIDS. 2004. *Substitution Maintenance Therapy in the Management of Opioid Dependence and HIV/AIDS Prevention: Position Paper*. Geneva, Switzerland: WHO.

UNAIDS (Joint United Nations Programme on HIV/AIDS). 2006. *2006 Report on the Global AIDS Epidemic: A UNAIDS 10th Anniversary Special Edition*. Geneva, Switzerland: UNAIDS.

Appendix A

Agenda for Information-Gathering Meeting, Geneva, December 2005

COMMITTEE ON THE PREVENTION OF HIV INFECTION AMONG INJECTING DRUG USERS IN HIGH-RISK COUNTRIES

December 19–20, 2005
Geneva, Switzerland

December 19, 2005

9:00–9:15 a.m. **Welcome, Introductions, and Opening Statement**

Hugh Tilson, M.D., Dr.PH.
Committee Chair

9:15–9:45 a.m. **Charge to the Committee**

Peter Piot, M.D., Ph.D.
Executive Director, UNAIDS
Under Secretary-General of the United Nations

9:45–10:15 a.m. **Overview of Addiction**

Michael Farrell, MRCPsych
Reader in Addiction Psychiatry,
National Addiction Centre,
Institute of Psychiatry, King's College, London

10:15–11:00 a.m. **Epidemiology of HIV/AIDS Among IDUs in High-Risk Countries and the Global Response**

Peter Ghys, M.D.
Acting Associate Director, Epidemic Monitoring and Prevention, Department of Policy, Evidence and Partnerships, UNAIDS

Catherine Anita Hankins, M.D., MSc, FRCPC
Associate Director of Policy, Evidence and Partnerships
Chief Scientific Adviser
UNAIDS

11:00–11:15 a.m. **Break**

11:15–12:45 p.m. **Evidence Regarding HIV Prevention for IDUs**

Overview:
Gerry V. Stimson Ph.D.
Emeritus Professor, Imperial College London, and
Executive Director, International Harm Reduction Association

Review of needle and syringe exchange programs:
Dr. Alex Wodak FRACP, FChAM
Director, Alcohol and Drug Service
St. Vincent's Hospital, Darlinghurst, Australia

Review of needle and syringe exchange programs:
Kerstin Käll, M.D., Ph.D.
Clinic for Dependency Disorders
University Hospital, Linköping, Sweden

Review of drug treatment strategies:
Michael Farrell, MRCPsych
Reader in Addiction Psychiatry,
National Addiction Centre,
Institute of Psychiatry, King's College, London

12:45–1:45 p.m. **Lunch**

1:45–3:15 p.m. **Country Perspectives Panel: Asian and Pacific Countries**

Zhang Fujie, M.D.
Director, Division of Treatment and Care
National Center for AIDS-STD Control and Prevention, Chinese Center for Disease of Control and Prevention

Adeeba Kamarulzaman, MBBS, FRACP
Head, Infectious Diseases Unit
Department of Medicine
University of Malaya Medical Centre, Malaysia

Chris Beyrer, M.D., M.P.H.
Associate Professor, Department of Epidemiology
Director, Johns Hopkins Fogarty AIDS International Training and Research Program
Director, Johns Hopkins Center for Public Health & Human Rights
Johns Hopkins Bloomberg School of Public Health
(discussing Thailand)

3:15–3:30 p.m. **Break**

3:30–5:45 p.m. **Country Perspectives Panel: Former Soviet States, Central, and Eastern European Countries**

Saulius Caplinskas, M.D., Ph.D.
Director, Lithuanian AIDS Centre
Assoc. Prof., Mykolas Romeris University

Monica Ciupagea M.D.
Program Officer
International Harm Reduction Development Program
Open Society Institute, Budapest

Oleg Tchestnov, M.D.
Deputy Director of the International Department
Ministry of Health, Russia

Ksenia Eroshina, M.P.H., Ph.D.
Head of Monitoring & Evaluation Department
Open Health Institute, Moscow, Russia

Alexey Mazus M.D.
Head of Moscow AIDS Center

Inga Upmace, M.D.
Deputy Director, AIDS Prevention Center, Latvia
Steering Committee member of CEE-HRN
(Central and Eastern Europe
Harm Reduction Network)

Lily Hyde
Harm Reduction and IEC Consultant
International HIV/AIDS Alliance in Ukraine

6:30 p.m. **Reception for all meeting participants at the ILO building, hosted by UNAIDS**

December 20, 2005

8:30–10:00 a.m. **Lessons Learned: Experiences in the United States, Canada, Australia, and Western European Countries**

Don C. Des Jarlais, Ph.D.
Director of Research, Baron Edmond de Rothschild Chemical Institute, Beth Israel Medical Center
Professor of Epidemiology, Department of Epidemiology and Population Health, Albert Einstein College of Medicine, New York

Alex Wodak, FRACP, FChAM
Director, Alcohol and Drug Service
St. Vincent's Hospital, Darlinghurst, Australia

Roel A. Coutinho, M.D., Ph.D.
Director, Centre for Infectious Disease Control
National Institute for Health and the Environment, The Netherlands

Gerry V. Stimson Ph.D.
Emeritus Professor, Imperial College London, and
Executive Director, International Harm Reduction Association

10:00–10:15 a.m. **Break**

10:15–12:30 p.m. **Illicit Drug Policies and the HIV Epidemic**

Andrew Ball, M.B., B.S., FChAM
Senior Strategy and Operations Advisor
Department of HIV/AIDS
World Health Organization

Christian Kroll
Senior Coordinator, HIV/AIDS Unit
Global Coordinator on HIV/AIDS
UNODC

Chris Beyrer, M.D., M.P.H.
Associate Professor, Department of Epidemiology
Director, Johns Hopkins Fogarty AIDS International Training and Research Program
Director, Johns Hopkins Center for Public Health & Human Rights
Johns Hopkins Bloomberg School of Public Health

Tomas Hallberg
Director, European Cities against Drugs (ECAD)
Stockholm, Sweden

George Zazulin
St. Petersburg Regional Director, ECAD, Russia

Alex Wodak, FRACP, FChAM
Director, Alcohol and Drug Service
St. Vincent's Hospital, Darlinghurst, Australia

Raminta Stuikyte
Director, Central and Eastern European Harm Reduction Network

12:30–1:30 p.m. **Lunch**

1:30–2:30 p.m. **Community Perspectives**

Mr. Loon Gangte (not able to attend; sent written remarks)
President, Delhi Network of Positive People, India
Regional Coordinator for South Asia
Collaborative Fund for HIV Treatment Preparedness

Mr. Samuel Nugraha
Partnership and Network Assistant
UNAIDS Secretariat Indonesia

2:30–3:00 p.m. **Methodological Considerations in Evaluating Evidence**

Don C. Des Jarlais, Ph.D.
Director of Research, Baron Edmond de Rothschild Chemical Dependency Institute, Beth Israel Medical Center
Professor of Epidemiology, Department of Epidemiology and Population Health, Albert Einstein College of Medicine, New York

3:00–3:30 p.m. **Public Comments**

3:30 p.m. **Adjourn**

Appendix B

Literature Search Strategies

This appendix discusses the Committee's strategy for collecting evidence on the effectiveness of HIV prevention interventions for injecting drug users. The Committee targeted its search to include studies of the effectiveness of sterile needle and syringe access programs, drug treatment (including pharmacotherapies and psychosocial interventions), and outreach interventions in reducing HIV infection and drug- and sex-related HIV risk behavior. A secondary objective was to identify studies examining the impact of these interventions on treatment-related outcomes and the use of health and social services, and any unintended consequences they might have.

METHODS FOR COLLECTING EVIDENCE

In gathering evidence, the Committee first drew on previous systematic reviews of the literature. These included the 1995 National Research Council/Institute of Medicine report, *Preventing HIV Transmission: The Role of Sterile Needles and Bleach;* the World Health Organization's Evidence for Action reports on access to sterile syringes, drug dependence treatment, and outreach; and recent reviews by the Cochrane Drug and Alcohol Review Group. Because the Committee's charge differed somewhat from the focus of these reviews, the Committee also conducted its own comprehensive search of the English language published (peer-reviewed) and unpublished literature (including conference abstracts and reports) on the effectiveness of HIV prevention interventions for IDUs.

To identify literature relating to sterile needle and syringe access programs, psychosocial interventions, and outreach, a research librarian searched the following databases from 1980 to January 2006: PubMed, EMBASE, PsycINFO, Cochrane, Grey Literature Report, Social Science Abstracts, Web of Science, and WorldCat.

In investigating psychosocial treatment, the Committee also considered evidence from two systematic reviews from the Cochrane Collaboration:[1]

- *Psychosocial Combined with Agonist Maintenance Treatments versus Agonist Maintenance Treatments Alone for Treatment of Opioid Dependence*
- *Psychosocial Treatment for Opiate Abuse and Dependence*

In evaluating the effectiveness of pharmacotherapies for opioid and stimulant dependence, the Committee relied primarily on evidence in several Cochrane reviews:

- *Substitution Treatment of Injecting Opioid Users for Prevention of HIV Infection*
- *Methadone Maintenance Therapy versus No Opioid Replacement Therapy for Opioid Dependence*
- *Buprenorphine Maintenance versus Placebo or Methadone Maintenance for Opioid Dependence*
- *LAAM Maintenance versus Methadone Maintenance for Heroin Dependence*
- *Oral Naltrexone Maintenance Treatment for Opioid Dependence*
- *Methadone Maintenance at Different Dosages for Opioid Dependence*
- *Antidepressants for Cocaine Dependence*
- *Treatment for Amphetamine Dependence and Abuse*
- *Carbamazepine for Cocaine Dependence*
- *Dopamine Agonists for Cocaine Dependence*

[1]The Cochrane Drug and Alcohol Review Group (the Review Group) is part of the Cochrane Collaboration, which was developed in the United Kingdom in 1992 with the goal of producing systematic reviews of the effects of various health care interventions that can be used by clinicians to guide their day-to-day practice. The Review Group conducts systematic reviews of primarily randomized clinical trials and controlled clinical trials of prevention, treatment, and rehabilitation interventions targeting drug dependence. To date, the Review Group has published over 30 reviews and 15 protocols. Available at: http://alcalc.oxfordjournals.org/cgi/content/full/36/2/109; http://www.cochrane.org/newslett/Drugs andAlcohol Autumn2005.pdf.

The Committee also reran the search strategies used in some of the Cochrane reviews from the publication date through February 2006. The Committee also considered the reference lists of key studies retrieved in the search, and unpublished data such as conference abstracts identified through the databases.

Together the Committee's searches generated some 10,000 titles. Two Committee members reviewed all these titles and excluded those obviously unrelated to the targeted interventions. Any title selected by one Committee member remained on the list. IOM staff and consultants then reviewed abstracts of these articles to determine whether they were appropriate for further consideration, using criteria developed by the Committee. A third party resolved any discrepancies, in consultation with the two reviewers.

Committee and staff members then extracted key aspects of these articles—including the study design, their outcome measures, and limitations on their results—for further examination by the Committee. The Committee then assessed the strength and quality of the evidence most relevant to the charge, using the framework described in Chapter 2.

SEARCH STRATEGIES

Drug Dependence Treatment

The Committee reran the search strategies from the following Cochrane reviews to identify new references published since the publication date:

- *Buprenorphine Maintenance versus Placebo or Methadone Maintenance for Opioid Dependence*
- *Methadone Maintenance Therapy versus No Opioid Replacement Therapy for Opioid Dependence*
- *Oral Naltrexone Maintenance Treatment for Opioid Dependence*
- *Psychosocial Combined with Agonist Maintenance Treatments versus Agonist Maintenance Treatments Alone for Treatment of Opioid Dependence*
- *Psychosocial Treatment for Opiate Abuse and Dependence*

Sterile Needle and Syringe Access

For this topic, the Committee modified search strategies appropriately for each database. The search strategy used on the PubMed database for sterile needle and syringe access is included below.

Search #1:

needle*[tiab] OR syringe*[tiab] OR needle exchange OR syringe exchange
AND
decontaminat*[tiab] OR contaminat*[tiab] OR distribut*[tiab] OR dispos*[tiab] OR disinfect*[tiab] OR exchang*[tiab] OR bleach*
AND
Harm reduction[tiab]
AND
hiv infections/pc OR hiv infections/transmission OR acquired immunodeficiency syndrome/pc OR acquired immunodeficiency syndrome/tm OR hiv seropositivity/pc OR hiv seropositivity/tm OR hiv[tiab] OR aids[tiab]

Search #2:

needle exchange OR syringe exchange
AND
hiv infections/pc OR hiv infections/transmission OR acquired immunodeficiency syndrome/pc OR acquired immunodeficiency syndrome/tm OR hiv seropositivity/pc OR hiv seropositivity/tm OR hiv[tiab] OR aids[tiab]
NOT
results of Search #1

Search #3:

[needle*[tiab] OR syringe*[tiab] OR needle exchange OR syringe exchange
AND
decontaminat*[tiab] OR contaminat*[tiab] OR distribut*[tiab] OR dispos*[tiab] OR disinfect*[tiab] OR exchang*[tiab] OR bleach*
AND
hiv infections/pc OR hiv infections/transmission OR acquired immunodeficiency syndrome/pc OR acquired immunodeficiency syndrome/tm OR hiv seropositivity/pc OR hiv seropositivity/tm OR hiv[tiab] OR aids[tiab]]
OR
[needle exchange OR syringe exchange
AND
hiv infections/pc OR hiv infections/transmission OR acquired immunodeficiency syndrome/pc OR acquired immunodeficiency syndrome/tm OR hiv seropositivity/pc OR hiv seropositivity/tm OR hiv[tiab] OR aids[tiab]]
NOT
results of Searches #1 OR #2

Search #4:

needle*[tiab] OR syringe*[tiab] OR needle exchange OR syringe exchange
AND
(risk* AND behav*) OR risk-taking[mh] OR risk factors[mh]
AND
hiv infections/prevention & control OR hiv infections/transmission OR acquired immunodeficiency syndrome/pc OR acquired immunodeficiency syndrome/tm OR hiv seropositivity/pc OR hiv seropositivity/tm OR hiv[tiab] OR aids[tiab]

Outreach and Psychosocial

The Committee used the following search strategy on the databases mentioned above to retrieve additional references related to outreach and psychosocial interventions:

1. substance-related disorders/ or exp opioid-related disorders/ or substance abuse, intravenous/
2. intravenous drug user?.mp.
3. injecting drug user?.mp.
4. injection drug use$.mp.
5. inject$ drug use$.mp.
6. 3 or 4
7. intravenous drug use$.mp.
8. 1 or 5 or 7
9. exp HIV/
10. exp hiv infections/ or acquired immunodeficiency syndrome/
11. HIV Seroprevalence/
12. 9 or 10 or 11
13. 8 and 12
14. prevention & control.fs.
15. pc.fs. or prevention.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
16. Primary Prevention/
17. (15 or 16) and 12
18. 17 and 8
19. exp psychotherapy/ or exp psychotherapy,brief/ or exp psychotherapy,group/ or exp psychotherapy,multiple/ or psychotherapy.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

20. exp cognitive therapy/ or exp social adjustment/ or exp socialization/ or exp teaching/ or social skill? training.mp. or adaptation,psychological/ or coping skill?.mp.
21. exp behavior therapy/ or self-control training.mp. or exp counseling/ or counseling.mp. or exp marital therapy/ or marital therapy.mp. or exp community mental health services/ or exp community networks/ or exp reinforcement,social/ or exp social support/ or community reinforcement.mp. or exp relaxation techniques/ or stress management.mp. or exp therapeutic community/ or therapeutic community.mp.
22. exp complementary therapies/ or exp "mind-body and relaxation techniques"/ or "biofeedback (psychology)"/
23. exp health education/ or patient education/
24. psychosocial intervention?.mp.
25. 19 or 20 or 21 or 22 or 24
26. 18 and 25
27. limit 26 to yr="1980 - 2006"
28. 13 and 25
29. limit 28 to yr="1980 - 2006"
30. Community-Institutional Relations/ or outreach.mp.
31. peer group/
32. "peer education".mp.
33. behavior$ prevention?.mp.
34. risk reduction behavior/
35. "risk reduction".mp.
36. "harm reduction".mp.
37. peer network?.mp.
38. 23 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39. 38 and 18
40. 27 or 39
41. 39
42. limit 41 to yr="1980 - 2006"

Appendix C

Country Case Examples

This appendix provides a series of case studies from individual countries selected from the regions that are the focus of this report. The cases demonstrate the wide range of policies and programs that are being implemented in an effort to control IDU-driven HIV epidemics. The purpose of this section is not to evaluate or compare performance or effectiveness, but rather to provide readers with a wide-angle view of the rich diversity of policies and programs being implemented worldwide. These case studies are not intended to be comprehensive, rather they represent summaries and expansion upon material provided to the Committee about individual national experiences that have helped to inform observations and recommendations about the complexities of implementing new programs.

The case studies of Iran, Malaysia, and China illustrate how countries with burgeoning HIV epidemics among IDUs have forged a compromise between a criminal justice approach and a public health approach to the dual epidemics of drug dependence and HIV among drug users. These experiences particularly informed the Committee's recommendation regarding the value of creating broad cross-sector consensus processes which permit those with conflicting perspectives to find the "common ground."

The fourth and fifth case studies, on Russia and Ukraine, show the impact of the legal and cultural context on policy, and the ability of a country to review and modify its policies on the basis of evolving lessons learned. They underscore the impact of stigma and the need to document and consider the unintended consequences of policy positions.

Likewise, finally, the case study on Thailand shows how a country modifies its policies and approaches as it addresses the changing drivers of its HIV epidemic.

IRAN

Iran sits directly on a key drug transit route running from Afghanistan to markets in the Persian Gulf, Turkey, Russia, and Europe (Nissaramanesh et al., 2005). Although non-injecting use of opium is more prevalent than injecting drug use, the country has an estimated 112,000 to 300,000 IDUs. HIV prevalence among IDUs ranges from 0.5 to 13.0 percent (Aceijas et al., 2004), and 60 to 70 percent of HIV transmission is IDU-related (Mokri, 2002).

After the 1979 Islamic Revolution, the country embarked on a tough anti-drug campaign that emphasized strict enforcement of new drug laws, the closure of treatment and detoxification programs, and the opening of compulsory rehabilitation camps (Nissaramanesh et al., 2005). Over the past 20 years, some 1.7 million Iranians have been imprisoned for drug offenses (State Welfare Organization, 2000, as cited in Nissaramanesh et al., 2005). However, in the 1990s, the policy changed to reflect the recognition that drug dependence is also a medical problem. Drug users who access treatment are now exempt from penal punishment and the country reopened short detoxification programs and created narcotics anonymous support groups and abstinence-based therapeutic communities (Nissaramanesh et al., 2005).

By the end of the 1990s, it became clear that these efforts were insufficient. The Iranian government encouraged its medical and public health experts to talk with drug treatment experts from other countries. This dialogue and several other factors led to a more comprehensive approach to reducing HIV transmission among drug users, including psychosocial services, opioid agonist maintenance therapy, drug-free treatment, and access to sterile needles and syringes (Nissaramanesh et al., 2005). Other factors leading to Iran's policy changes included the advocacy role of nongovernmental organizations and civil society, the cooperation between the Ministry of Health, the prison department health authorities, and other stakeholders on drug treatment and HIV/AIDS, and the education of senior policymakers regarding HIV prevention for IDUs (Razzaghi et al., 2006).

In 2000, Iran began its first pilot methadone project in a psychiatric hospital, and in 2002 a major outpatient methadone maintenance program opened in Tehran. Other maintenance treatment programs have since started in other parts of the country, although buprenorphine is not yet widely available outside of special research and demonstration programs. The Ministry of Health has expressed satisfaction with these projects and is

drafting national guidelines for methadone maintenance treatment (Nissaramanesh et al., 2005). The Welfare Organization and Ministry of Health have supported private centers directed by general practitioners that offer methadone and buprenorphine maintenance treatment along with detoxification and abstinence-based interventions. More than 600 private centers now operate nationwide, and up to 600 more centers have been recommended. Narcotics Anonymous, an abstinence-based 12-step program, is also widely used in Iran, with some 20,000 participants (Personal communication, A. Mokri, May 4, 2006).

Drug users and IDUs account for a significant proportion of the Iranian prison population. In 2003, prison authorities initiated an HIV prevention program, and some 40 prison clinics now provide drug treatment, including methadone maintenance therapy, and HIV prevention services (Nissaramanesh et al., 2005).

Iran has recently initiated a network of some 60 community-based drop-in centers that provide basic health care as well as information on HIV risk, condoms, and, in some cases, clean needles and syringes (Nissaramanesh et al., 2005). A growing number of nongovernmental organizations also offer counseling, other abstinence-based treatments, family education, and even inpatient care.

Clean needles and syringes are provided through drop-in centers, although the number of IDUs using this service is unclear. The Iranian government expressed support for needle and syringe exchange in an executive order in January 2005 (Nissaramanesh et al., 2005).

Overall, although Iran still sees drug dependence as a crime, the broad range of HIV prevention services targeting drug users reflects a shift from a strictly punitive approach to one that includes drug treatment and HIV prevention.

MALAYSIA

Malaysia has some of the world's harshest drug laws and enforcement practices. According to the Dangerous Drug Act of 1952—revised in 1983 (Treatment and Rehabilitation Act)—any person who is guilty of consuming or administering certain amounts of a long list of drugs is subject to mandatory 2-year treatment and rehabilitation. The same law makes carrying injecting equipment without a prescription illegal (Kamarulzaman, 2005).

Malaysia's self-declared goal is to become a "drug-free society by 2015," and in 2003 the government launched a campaign, which identified IDUs as a principal target (Reid et al., 2005). The country initially viewed needle exchange and opioid agonist maintenance programs as undermining this strong drug control policy and its goal of becoming drug-free (Reid et

al., 2005). However, a major policy shift has occurred over the past 2 years, as Malaysia's response to its IDU-driven HIV epidemic has evolved from a primarily criminal justice model to one that includes public health interventions. Key factors driving the transition include:

- An awareness of the escalating HIV crisis. Malaysia reported some 65,000 HIV cases at the end of 2004—up from near zero in 1990—and about 75 percent of all cases are attributable to IDUs (Reid et al., 2005).[1]
- Malaysia's commitment to achieving all eight of the United Nation's Millennium Development Goals—one of which is reducing the incidence of HIV/AIDS (Kamarulzaman, 2005).
- An evaluation of the country's mandatory 2-year detention for drug use, which showed high relapse rates among drug users after release from detention (Reid et al., 2005).[2]
- A provision in Islam, the major religion in Malaysia, that tolerates individual harm (such as the provision of clean needles and opioid agonist maintenance treatment to IDUs) to prevent harm to a population (an HIV epidemic) and that tolerates a lesser harm in order to eliminate a greater harm (Kamarulzaman, 2005).

In October 2005, the government launched a free pilot methadone maintenance project for 1,200 patients. In January 2006, Malaysia also initiated a pilot government-sponsored needle exchange and outreach program (Kamarulzaman, 2005). The country began allowing the use of buprenorphine for opioid maintenance therapy in 2001, and private general practitioners now administer the treatment to about 20,000 heroin users. However, imports of buprenorphine are limited to 12 kilograms per year (Personal communication, M. Mahmud, May 8, 2006). Thus Malaysia represents a nation learning from its experience in balancing policies to combat drug abuse and the spread of HIV among IDUs.

CHINA

China's HIV epidemic has been concentrated among injecting drug users, except in several central provinces where blood selling was the driving force. All 31 provinces and autonomous regions have reported HIV

[1]However, that could be an overestimate because the recording of arrested and incarcerated IDUs is mandatory. Other than pregnant women and blood donors, who are routinely screened, there is no surveillance of any other HIV-infected population (such as sex workers).

[2]Officially, Malaysia has some 900,000 illicit drug users, including both IDUs and non-IDUs. The country has 28 drug rehabilitation centers, with HIV rates of 16–18 percent. The centers house between 10,000 and 14,000 drug users each year.

infection among IDUs. Although HIV prevalence is difficult to estimate because the IDU population is often hidden, it exceeds 50 percent among IDUs in some areas of Xinjiang, Yunnan, and Sichuan (Ministry of Health PRC et al., 2006). Sexual transmission has also risen substantially in the past few years, and emerging evidence shows that HIV has begun spreading to the general population.

Opiate abuse has existed in China since the 16th century. According to one estimate, some 200 million persons were opium abusers before the founding of the People's Republic of China (PRC) in 1949 (China UN Theme Group on HIV/AIDS and Ministry of Health PRC, 1997). In 1950, the Chinese government launched an extensive campaign against drug abuse and drug trafficking, and nearly wiped out opium abuse within 3 years. However, when China began to open its borders and change its economic structure in 1980, opium and heroin began to enter the country from the Golden Triangle region. While the government is still committed to eradicating drug abuse, the country is home to about 2 million IDUs (China UN Theme Group on HIV/AIDS and Ministry of Health PRC, 1997). Rapid changes in methods for administering heroin—from smoking or inhaling to injecting—have greatly increased the likelihood that HIV, hepatitis, and other infectious diseases will spread.

Although a powerful and well-funded policy emphasizes the arrest and confinement of IDUs, the rise of HIV among IDUs convinced the Chinese government to permit pilot needle and syringe exchange (NSE) programs. The government currently funds 91 such programs, and international donors have funded others (Office of the State Council Working Committee on AIDS in China, 2005). Since 2004, the China State Council has issued official statements supporting needle and syringe exchange, methadone maintenance treatment, and other community-based HIV prevention strategies. The Council's HIV/AIDS Working Committee has also coordinated interagency efforts—including between public health authorities and police—to prevent HIV transmission among IDUs, and made such work a high priority.

Also in 2004, after strong advocacy by key scientists at the China Centers for Disease Control, the government launched an ambitious methadone maintenance program. By the end of 2005, 128 government-supported methadone maintenance treatment sites were serving more than 8,000 clients (Office of the State Council Working Committee on AIDS in China, 2005). The program aims to establish 1,000 to 1,500 sites serving 200,000 to 300,000 clients by 2008. Government funding is available for methadone maintenance treatment programs in urban areas, and for needle and syringe exchange in rural areas.

Despite these encouraging signs, there are tensions and inconsistencies between criminal justice and public health policies that have operational

implications. For example, in southern Guangxi Province, police—as directed by provincial and local authorities—have supported a cross-border HIV prevention project that provides peer education and NSE. Yet police have also intensified crackdowns on drug users, committing growing numbers to detoxification centers and labor camps and driving many others underground. These activities have had a chilling effect on the willingness of IDUs to meet with peer educators and receive sterile injecting equipment: the average number of needles/syringes the cross-border project provides each month dropped from 12,000 in 2003 to 8,000 in 2005 (Personal communication, T. Hammett, Abt Associates, June 30, 2006). IDUs who receive fewer sterile needles/syringes are more likely to share equipment and put themselves and others at higher risk for HIV.

These tensions may gradually subside, given that Chinese policies for preventing and controlling HIV transmission have become much more pragmatic. Methadone maintenance treatment and NSE—almost unimaginable several years ago—are expanding across the country. This trend may accelerate as the Chinese economy continues to integrate with international markets, but the country still recognizes the need to balance and, to the extent possible, harmonize the policy environment.

RUSSIA

HIV prevalence in Russia remained low until the mid-1990s, when HIV entered the IDU population. The epidemic has since expanded, with outbreaks in 82 of the 89 oblasts (regions) over the past decade. Official Russian data show about 350,000 people living with HIV/AIDS as of the end of 2005 (Ladnaya, 2005 as cited in UNAIDS, 2006).[3] However, the latest estimates from UNAIDS say that as many as 560,000 to 1,600,000 people are now living with HIV (UNAIDS, 2006). Increasingly, HIV is spreading from IDUs to their non-injecting sexual partners and beyond, suggesting that the HIV epidemic—once concentrated among IDUs—is becoming more generalized (UNAIDS, 2006).

After the Soviet Union dissolved in 1991, Russia adopted strict criminal codes on the use of illicit drugs in the face of rapidly escalating numbers of IDUs (Klein et al., 2004). The Russian Ministry of Health estimates that there are between 0.5 and 1.5 million drug users in Russia, with as many as 6 million people reporting drug use at some point in their lifetime.[4] Laws passed in 1998 and 2001 incorporated the three United Nations drug con-

[3]Data also available in Russian at http:/hivrussia.org/stat [accessed August 23, 2006].

[4]Data online (in Russian). Available at: http://www.medlinks.ru [accessed August 23, 2006].

trol conventions[5] and contained several articles on narcotics. These laws set very low thresholds for possession of illicit drugs punishable by mandatory imprisonment. For example, purchases of 0.005 grams of heroin—one-hundredth of an average daily dose—were punishable by 5 to 7 years in prison. As a result, today about one-third of prisoners in the country's penal system are serving time for drug charges.

However, legislative changes since 2003 have reshaped the policy context for IDUs. Compulsory drug treatment is prohibited, and penalties for small-scale drug possession have been relaxed. In May 2004, Russia amended the Criminal Code so that possession of up to 10 times the "average single dose" (equivalent to 1.0 grams) is no longer a criminal offense, and possession of 10 to 15 times the average single dose is punishable by a fine and community service. Punishment for drug sales is harsher than in the past, reflecting a trend toward imposing stricter penalties on drug dealers as opposed to drug users. In 2005, because of lobbying by the Federal Drug Control Service, the legislation was again revised to amend the "average single dose."

The 1998 and 2001 legislation forbade the use of opioid agonist maintenance treatment for drug dependence, including methadone and other long-term pharmacotherapy programs. This reflects the position of Russian professional narcotics community, which does not accept opioid agonist maintenance as treatment (Personal communication, V.N. Krasnov, Russian Society of Psychiatrists, June 16, 2006). As a result, the traditional drug treatment system in Russia is abstinence oriented.

In the face of the tensions between the law enforcement approach and the public health approach, progress has been made. A peer-outreach counseling program (without needle exchange) in Moscow funded by Médecins Sans Frontières distributed leaflets and condoms to some 10,000 IDUs in 1997—a figure that grew by 50 to 250 per month during the following 2 years. However, referrals to drug treatment and HIV testing facilities were low, as IDUs did not want to become registered as drug users because of potential consequences regarding employment and housing status (Platt et al., 2004). Nonetheless, the program became a model for other HIV prevention programs aimed at IDUs, and received broad attention from the Ministry of Health and the Russian media (UNAIDS and UNDCP, 2001) Other HIV prevention activities include a peer-driven intervention in Yaroslavl, a mobile syringe exchange project in Moscow, and a mobile education and syringe project in St. Petersburg (Rhodes et al., 2004; Sergeyev et al., 1999; UNAIDS and UNDCP, 2001).

[5]UN drug control conventions available at: http://www.unodc.org/unodc/drug_and_crime_conventions.html.

As of February 2003, nearly all of the estimated 75 documented HIV prevention programs for IDUs included needle and syringe exchange, and one study found that more than half the projects surveyed operated mobile outreach services. However, coverage remains restricted: results from another survey suggest that 65 percent of the needle and syringe exchanges in Russia reach less than 1 percent of the local IDU population, and that fewer than 5 percent of NSEs reach more than 5 percent of their local IDU population (Burrows, 2001). Thus Russia continues to balance the tradeoffs between ensuring quality of individual programs and dissemination for public health impact.

UKRAINE

Ukraine has one of the most significant HIV/AIDS epidemics in Europe, with a mean estimated HIV prevalence in excess of 1 percent among people aged 15 to 49 years (Bernitz and Rechel, 2006). Ukraine is home to an estimated 560,000 IDUs (Nikolaevich et al., 2003)—8.5 percent to 9.6 percent of whom are thought to be HIV-seropositive (Aceijas et al., 2004). Sentinel surveillance data suggest HIV-prevalence rates among IDUs range from 12 percent to 38 percent in Ukrainian cities (Bernitz and Rechel, 2006). As a result of high rates of sex workers who are also IDUs, sexual transmission of HIV is closely tied with transmission through shared injecting equipment (Dehne and Kobushche, 2000; Kyrychenko and Polonets, 2005). HIV transmission is also common among Ukrainian prison populations (Bollini, 2001).

IDUs in Ukraine mainly inject liquid poppy straw and liquid amphetamine, typically purchased as pre-loaded syringes from drug dealers (Booth et al., 2006). Heroin use has also been observed, given that Ukraine lies on the drug route from Afghanistan into Western Europe (U.S. Department of State, 2001).

Although Ukraine, much like Russia, previously emphasized criminalization of drug use, it has emphasized a greater commitment to HIV prevention in recent years. Legislation on HIV/AIDS guarantees the right to information on HIV, and the country has abandoned mandatory testing for some groups (e.g., sex workers and IDUs) in favor of voluntary testing. State commitment to HIV prevention programs includes needle and syringe exchange and opioid agonist maintenance using buprenorphine which was identified as an important objective by the National AIDS Program (Human Rights Watch, 2006). Needle and syringe exchange is not illegal, nor are needle possession and purchase, and needles can be readily purchased from pharmacies (Human Rights Watch, 2006).

Despite the legislative steps, implementation of actual programs has tended to be slow, except for needle and syringe exchange and a related

package of interventions. Some 300 exchange points—mainly operated by nongovernmental organizations and funded by international agencies such as the Global Fund—now reach about 70,000 IDUs (Human Rights Watch, 2006). NSE sites typically also provide information, counseling, and referrals to other services.

Government-run clinics use injectable buprenorphine on a small scale for detoxification and 6-month opioid agonist maintenance treatment serving an estimated 650 patients. In 2004, sublingual buprenorphine was introduced on a pilot basis in government facilities in two cities. In September 2005 sublingual buprenorphine was expanded further, with Global Fund support, to 200 patients in seven cities. However, opposition to opioid agonist therapy from law enforcement agencies and agencies involved with narcotic drugs seems to be significant (Human Rights Watch, 2006). The scale of opposition is particularly serious for methadone, which is not currently in use by treatment programs in Ukraine.

Efforts to learn from evolving experiences and implement new policies across sectors continue.

THAILAND

Thailand is one of the few countries in the world to have successfully reversed its heterosexual HIV epidemic, after having launched a massive education and condom campaign aimed at sex workers and their clients (Phoolcharoen et al., 1998). The country's "100% condom use campaign" is lauded as a model effort to control HIV through collaboration among government agencies, law enforcement officials, public health authorities, and private groups (Perngmark et al., 2003). Thailand is also one of the first developing or transitional countries to have implemented an effective perinatal HIV prevention campaign, by scaling up use of the antiretroviral drug AZT (Amornwichet et al., 2002).

Although HIV prevalence has dropped as much as four-fold across Thailand, injecting drug use has emerged as a major risk factor for HIV transmission. For example, even as HIV prevalence among 21-year-old male military conscripts fell from 11.4–11.9 percent in 1991–1993 to 2.4 percent in 1998, the percentage of HIV-seropositive men with a history of drug use rose from 1 percent in 1991 to 25.8 percent in 1998 (Nelson et al., 2002). Over the past several years, national surveys have reported HIV prevalence rates among IDUs of 30 and 50 percent. Southern Thailand—which has minimal HIV prevention services for IDUs—has reported the highest rates (Perngmark et al., 2003).

Within the emerging IDU-driven HIV epidemic, incarceration has been shown to be an independent risk factor for HIV seroconversion: that is, incarcerated IDUs are more likely to become infected than non-incarcerated

IDUs (Choopanya et al., 2002; Dolan et al., 2003). This trend is not unique to Thailand (Rahbar et al., 2004), but no reported HIV prevention programs in Thailand target incarcerated IDUs (Rahbar et al., 2004).

Thailand is known for its strict enforcement of drug laws, and its 2003 crackdown on illicit drug use—which led to the death of more than 2,000 people—attracted international attention. A rapid expansion of the use of "yaba," as amphetamines in tablet form are known in Thailand, prompted the crackdown. (Kulsudjarit, 2004; Beyrer et al., 2004). Sources showed obvious declines in the use of both methamphetamine and heroin in rural areas after the drug war (Vongchak et al., 2005; Poshyachinda et al., 2005).

In the face of these aggressive policies against drugs, HIV prevention strategies for IDUs in Thailand have evolved to varying degrees. Outreach and education have the longest history, as the Ministry of Public Health has been using media campaigns to disseminate information on HIV transmission through needle sharing since the early 1990s (Perngmark et al., 2003). Needle exchange and bleach distribution have begun on a pilot basis in Bangkok and some areas of northern Thailand (Gray, 1995; Vanichseni et al., 2004). In southern Thailand, while no needle and syringe exchange exist, IDUs can purchase equipment legally and at very low cost from area pharmacies (Perngmark et al., 2003). District hospitals nationwide offer short-term, tapered methadone treatment, although many addicts eventually resume drug use and return to the clinic (Saelim et al., 1998). Few clinics, most of which are in Bangkok, offer long-term maintenance therapy (Choopanya et al., 2003). The recently unveiled national HIV/AIDS plan for Thailand noted that HIV prevention interventions for IDUs including needle and syringe exchange, opioid agonist maintenance, and outreach, will be expanded and made accessible throughout the country (Thailand Ministry of Public Health, 2006).

REFERENCES

Aceijas C, Stimson GV, Hickman M, Rhodes T. 2004. Global overview of injecting drug use and HIV infection among injecting drug users. *AIDS*. 18(17):2295–2303.

Amornwichet P, Teeraratkul A, Simonds RJ, Naiwatanakul T, Chantharojwong N, Culnane M, Tappero JW, Kanshana S. 2002. Preventing mother-to-child HIV transmission: The first year in Thailand's national program. *Journal of the American Medical Association*. 288:245–248.

Bernitz B, Rechel B. 2006. HIV data in central and Eastern Europe: Fact or fiction? In Matic S, Lazarus J, Donoghoe M, eds. *HIV/AIDS in Europe: Moving from Death Sentence to Chronic Disease Management*. Copenhagen, Denmark: WHO Regional Office for Europe. Pp. 232–242.

Beyrer C, Razak MH, Jittiwutikarn J, Suriyanon V, Vongchak T, Srirak N, Kawichai S, Tovanabutra S, Rungruengthanakit K, Sawanpanyalert P, Sripaipan T, Celentano DD. 2004. Methamphetamine users in Northern Thailand: Changing demographics and risks for HIV and STD among treatment-seeking substance abusers. *International Journal of STDs and AIDS*. 15(10):697–704.

Bollini P, ed. 2001. *HIV in Prisons: A Reader with Particular Relevance to Newly Independent States*. Geneva, Switzerland: WHO.

Booth R, Kwiatkowski C, Mikulich-Gilbertson S, Brewster J, Salomonsen-Sautel S, Corsi K, Sinitsyna L. 2006. Predictors of risky needle use following interventions with injection drug users in Ukraine. *Drug and Alcohol Dependence*. 82(Suppl. 1):S49–S55.

Burrows D. 2001. *A Best Practice Model of Harm Reduction in the Community and in Prisons in the Russian Federation: Final Project Report*. Washington, DC: World Bank.

China UN Theme Group on HIV/AIDS and Ministry of Health, People's Republic of China (PRC). 1997. *China Responds to AIDS: HIV/AIDS Situation and Needs Assessment Report*. Beijing: China UN Theme Group on HIV/AIDS and Ministry of Health, People's Republic of China.

Choopanya K, Des Jarlais DC, Vanichseni S, Kitayaporn D, Mock PA, Raktham S, Hireanras K, Heyward WL, Sujarita S, Mastro TD. 2002. Incarceration and risk for HIV infection among injection drug users in Bangkok. *Journal of Acquired Immune Deficiency Syndromes*. 29(1):86–94.

Choopanya K, Des Jarlais DC, Vanichseni S, Mock PA, Kitayaporn D, Sangkhum U, Prasithiphol B, Hiranrus K, van Griensven F, Tappero JW, Mastro TD. 2003. HIV risk reduction in a cohort of injecting drug users in Bangkok, Thailand. *Journal of Acquired Immune Deficiency Syndromes*. 33(1):88–95.

Dehne K, Kobushche Y. 2000. *The HIV/AIDS Epidemic in Central and Eastern Europe: Update 2000*. Geneva, Switzerland: UNAIDS.

Dolan K, Rutter S, and Wodak AD. 2003. Prison-based syringe exchange programmes: A review of international research and development. *Addiction*. 98:153–158

Gray J. 1995. Operating needle exchange programmes in the hills of Thailand. *AIDS Care*. 7(4):489–499.

Human Rights Watch. 2006. *Rhetoric and Risk: Human Rights Abuses Impeding Ukraine's Fight Against HIV/AIDS*. [Online]. Available: http://hrw.org/reports/2006/ukraine0306/ [accessed August 22, 2006].

Kamarulzaman A. 2005 (December 19). *Country Perspective: Malaysia*. Presentation at the Institute of Medicine Workshop on the Prevention of HIV Among Injecting Drug Users in High-Risk Countries, Geneva, Switzerland. Institute of Medicine Committee on the Prevention of HIV Infection Among Injecting Drug Users in High-Risk Countries.

Klein A, Roberts M, Trace M. 2004. *Drug Policy and the HIV Pandemic in Russia and Ukraine*. [Online]. Available: http://www.internationaldrugpolicy.net/reports/Beckley Foundation_BriefingPaper_02.pdf [accessed August 22, 2006].

Kulsudjarit K. 2004. Drug problem in southeast and southwest Asia. *Annals of the New York Academy of Science*. 1025:446–457.

Kyrychenko P, Polonets V. 2005. High HIV risk profile among female commercial sex workers in Vinnitsa, Ukraine. *Sexually Transmitted Infections*. 81:187–188.

Ladnaya NN. 2005 (December 15–16). *HIV/AIDS Epidemiological Situation in Russia*. Presentation to the Meeting on Universal Access to HIV Prevention, Treatment, Care and Support in the Russian Federation.

Ministry of Health, People's Republic of China (PRC), Joint United Nations Programme on HIV/AIDS, World Health Organization. 2006. *2005 Update on the HIV/AIDS Epidemic and Response in China*. Beijing, China: National Center for AIDS/STD Prevention and Control.

Mokri A. 2002. Brief overview of the status of drug abuse in Iran. *Archives of Iranian Medicine*. 5(3):184–190.

Nelson KE, Eiumtrakul S, Celentano DD, Beyrer C, Galai N, Kawichai S, Khamboonruang C. 2002. HIV infection in young men in northern Thailand, 1991–1998: Increasing role of injection drug use. *Journal of Acquired Immune Deficiency Syndromes*. 29(1):62–68.

Nikolaevich V, Vitalievich V, Vasilievich D. 2003. *Application of Substitutive Therapy in the Course of Treatment and Rehabilitation of Those Having Opioid Addiction Syndrome: Methodological Recommendations*. Kiev, Ukraine: Ministry of Health, Scientific Medical Information and Patent and License Operations Ukrainian Center.

Nissaramanesh B, Trace M, Roberts M. 2005. *The Rise of Harm Reduction in the Islamic Republic of Iran*. [Online]. Available: http://www.internationaldrugpolicy.net/reports/BeckleyFoundation_BriefingPaper_08.pdf [accessed August 22, 2006].

Office of the State Council Working Committee on AIDS in China. 2005. *Progress on Implementing UNGASS Declaration of Commitment in China 2005*. [Online]. Available: http://data.unaids.org/pub/Report/2006/2006_country_progress_report_china_en.pdf [accessed June 30, 2006].

Poshyachinda V, Ayudhya SNA, Aramrattana A, Kanato M, Assanangkornchai S, Jitipiromsri S. 2005. Illicit substance supply and abuse in 2000–2004: An approach to assess the outcome of the war on drug operation. *Drug and Alcohol Review*. 24:461–466.

Perngmark P, Celentano DD, and Kawichai S. 2003. Needle sharing among southern Thai drug injectors. *Addiction*. 98:1153–1161.

Phoolcharoen W, Ungchusak K, Sittitrai W, Brown T. 1998. Thailand: Lessons from strong national response to HIV/AIDS. *AIDS*. 12(Suppl B):S123–S135.

Platt L, Hickman M, Rhodes T, Mikhailova L, Karavashkin V, Vlasov A, Tilling K, Hope V, Khutorksoy M, Renton A. 2004. The prevalence of injecting drug use in a Russian city: Implications for harm reduction and coverage. *Addiction*. 99:1430–1438.

Rahbar AR, Rooholamini S, Khoshnood K. 2004. Prevalence of HIV infection and other blood-borne infections in incarcerated and non-incarcerated injection drug users (IDUs) in Mashhad, Iran. *International Journal of Drug Policy*. 15:151–155.

Razzaghi E, Nissaramanesh B, Afshar P, Ohiri K, Claeson M, Power R. 2006. HIV/AIDS harm reduction in Iran. *Lancet*. 368:434–435.

Reid G, Kamarulzaman A, Kaur Sran S. 2005. *Rapid Situation Assessment of Malaysia*. Kuala Lumpur, Malaysia: University of Malaya, Department of Medicine, Infectious Disease Unit.

Rhodes T, Sarang A, Bobrik A, Bobkov E, Platt L. 2004. HIV transmission and HIV prevention among injecting drug users in Russia. *International Journal of Drug Policy*. 15(1): 1–16.

Saelim A, Geater A, Chongsuvivatwong V, Rodkla A, Bechtel GA. 1998. Needle sharing and high-risk sexual behaviors among IV drug users in southern Thailand. *AIDS Patient Care and STDs*. 12:707–713.

Sergeyev B, Oparina T, Rumyantseva TP, Volkanevskii VL, Broadhead RS, Heckathorn DD, Madray H. 1999. HIV prevention in Yaroslavl, Russia: A peer-driven intervention and needle exchange. *Journal of Drug Issues*. 29(4):777–804.

State Welfare Organization. 2000. Drug abuse prevention in youth needs a National movement. Tehran, Iran: State Welfare Organization (unofficial translation).

Thailand Ministry of Public Health. 2006 (May 31-June 2). *Towards Universal Access by 2010: Thailand National HIV and AIDS Program. Reduce New HIV Infection by Half in 2010*. Presentation at the high-level meeting and comprehensive review of the progress achieved in realizing the targets set out in the Declaration of Commitment on HIV/AIDS. New York: The United Nations.

UNAIDS. 2006. *Report on the Global AIDS Epidemic*. Geneva, Switzerland: UNAIDS.

UNAIDS and UNDCP (United Nations International Drug Control Program). 2001. *Drug Abuse and HIV/AIDS: Lessons Learned—Case Studies in Central Eastern Europe and Central Asia*. New York: United Nations.

U.S. Department of State. 2001. *2000 International Narcotics Control Strategy Report (INCSR)*. [Online]. Available: http://www.state.gov/p/inl/rls/nrcrpt/2000/ [accessed June 30, 2006].

Vanichseni S, Des Jarlais DC, Choopanya K, et al. 2004. Sexual risk reduction in a cohort of injecting drug users in Bangkok, Thailand. *Journal of Acquired Immune Deficiency Syndromes*. 37(1):1170–1179.

Vongchak T, Kawichai S, Sherman S, Celentano D D, Sirisanthana T, Latkin C, Wiboonnatakul K, Srirak N, Jittiwutikarn J, Aramrattana A. 2005. The influence of Thailand's 2003 "war on drugs" policy on self-reported drug use among injection drug users in Chiang Mai, Thailand. *International Journal of Drug Policy*. 16:115–121.

Appendix D

Tables Summarizing the Evidence on Multi-Component HIV Prevention Programs That Include Needle and Syringe Exchange (NSE)

TABLE D-1 Case-Control Studies

Study	Description	Sample Size (n)
***Hagan et al., 1995**	Examines the association between use of syringe exchange and hepatitis B and C in IDUs.	Cases: 28 IDUs with acute hepatitis B; 20 IDUs with acute hepatitis C. Controls: IDUs with no markers of exposure to hepatitis B or C (n=38 and 26, respectively).
***Patrick et al., 1997**	Identifies determinants of HIV seroconversion among IDUs during a period of rising prevalence in Vancouver despite the prevalence of NSE and outreach.	Cases: IDUs with a new positive HIV test after January 1, 1994, and a negative test within the prior 18 months (n=89). Controls: required 2 negative tests during the same period (n=192).

Outcome Measures	Results	Limitations
Syringe exchange use; hepatitis B and C infection.	75% of case patients with hepatitis B and 26% of control subjects had never used the exchange; similar proportions were found for the hepatitis C case and control groups. After adjustment for demographic characteristics and duration of drug use, nonuse of the exchange was associated with a six-fold greater risk of hepatitis B (OR=5.5; 95% CI: 1.5–20.4) and a sevenfold greater risk of hepatitis C (OR=7.3; 95%CI: 1.6–32.8).	• Source population were IDUs in Pierce County (Washington) and were at risk for developing hepatitis B or C. • May have been differences between the injection practices of cases and controls which may have resulted in uncontrolled confounding. • Cases and controls may have differed in their use of other strategies (bleach, syringe purchase in pharmacies, etc.) to prevent infection. • The Tacoma syringe exchange's role as the primary source of HIV prevention for local IDUs may have contributed to the magnitude of the association between syringe exchange and risk of viral hepatitis.
Determinants of HIV seroconversion.	Multivariate analysis showed borrowing syringes, unstable housing, and injecting ≥ 4 times daily to be independently associated with seroconversion. Protective associations were found between sex with opposite gender and tetrahydrocannabinol use.	• Cases may have had differential recall of events than controls. • Self-reported data. • Study focused on incident cases of HIV and systematically excluded populations in which HIV is already highly prevalent. • Statistical power was limited with respect to ability to do subgroup analyses.

continued

TABLE D-1 Continued

Study	Description	Sample Size (n)
van Ameijden et al., 1992	Assesses risk factors for HIV seroconversion among IDU and investigates if HIV prevention services in Amsterdam have a protective effect on HIV seroconversion.	Cases: 31 IDU seroconverters Controls: 202 seronegative IDUs

*Indicates an article selected by the Committee for relevance or sound study design.

Outcome Measures	Results	Limitations
HIV seroconversion	No evidence was found that receiving daily methadone treatments at methadone posts and obtaining new needles/ syringes via the NSE were protective. Three independent risk factors for seroconversion were found in logistic regression: living >10 years in Amsterdam (OR=2.45; 95% CI: 1.09–5.53); first injection less than/equal to 2 years ago (OR=3.43; 95% CI: 1.20–9.81); and injecting mainly at home (OR=0.39; 95% CI: 0.18–0.88).	• Self-reported data. • Small statistical power and the need to dichotomize most variables because of the small number of seroconverters. • Only persons who visited two times or more were included, and these persons may be different from those who visited only once or those who never visited.

TABLE D-2 Prospective Cohort Studies

Study	Description	Sample Size (n)
***Bluthenthal et al., 2000**	Determines whether use of syringe exchange is associated with cessation of syringe sharing among high-risk injecting drug users.	340 high-risk injection drug users.
***Bruneau et al., 1997**	Assesses the association between risk behavior and HIV seroprevalence and seroincidence among IDUs in Montreal. The association was examined in three risk assessment scenarios using intensive covariate adjustment for confounders: a cross-sectional analysis of NSE use at entry as a determinant of sero-prevalence; a cohort analysis of NSE use at entry as a predictor of subsequent seroconversion; and a nested case-control analysis of NSE participa-tion during follow-up as a predictor of seroconversion.	974 HIV-negative IDUs.

Outcome Measures	Results	Limitations
Syringe sharing; use of syringe exchange.	At follow-up interview, 60% reported quitting syringe sharing. IDUs who began using the syringe exchange were more likely to quit sharing syringes (AOR=2.68; 95% CI: 1.35–5.33), as were those who continued using the syringe exchange program (AOR=1.98; 95% CI: 1.05–3.75).	• Participants not randomly selected. • Biases associated with self-reported data regarding sensitive and stigmatized behavior. • Comparison group was made up of IDUs at high risk who reside in a community with syringe access limited to NSE.
HIV seroprevalence and seroincidence.	In the cohort study, there were 89 incident cases of HIV infection, with a cumulative probability of HIV seroconversion of 33% for NSE users and 13% for nonusers ($p<0.0001$). In the nested case-control study, consistent NSE use was associated with HIV seroconversion during follow-up (OR=10.5; 95% CI: 2.7-41.0).	• Study is observational and was not specifically designed to evaluate the efficacy of NSE in preventing HIV infection. • Findings not generalizable because of the type of recruitment and the differences between participants and those lost to follow-up. • Possible misclassification bias.

continued

TABLE D-2 Continued

Study	Description	Sample Size (n)
***Bruneau et al., 2004**	Identifies factors associated with sustained cessation of injection, and examines the relationship between sustained cessation and prior injection frequency between 1995 and 1999 in Montreal.	1,004 IDUs.
Cox et al., 2000	Presents findings of an Irish follow-up study to establish the effectiveness of syringe exchanges as a strategy to prevent HIV in IDUs.	370 IDUs who attended the Merchants Quay Projects Health Promotion Unit, between May 1997 and October 1998.

Outcome Measures	Results	Limitations
Sustained injection cessation.	18.5% of IDUs reported a period of sustained injection cessation during the study period. Attending NSEs or pharmacies appeared to be a modifier of the relation between cessation and prior injection frequency. (OR=0.68; 95% CI: 0.42–1.12) for IDUs who injected 30–100 times in the month prior to interview and attended NSEs or pharmacies. (OR=0.07; 95% CI: 0.01–0.30) for IDUs who did not use these services.	• Majority of study participants were cocaine addicts. • Self-reported data. • Possible misclassification bias of outcome and exposure. • Source population was dependent upon self-selection.
Frequency of injection; needle sharing; condom use.	Significant reduction in the frequency of injection; evidence of positive behavior change in relation to improved injection practices. No substantial change in respondents' self-reported sharing of injecting paraphernalia or condom use.	• Self-reported data. • Possible selection bias.

continued

TABLE D-2 Continued

Study	Description	Sample Size (n)
Des Jarlais et al., 1996	Uses meta-analytic techniques to combine HIV incidence data from three studies: the Syringe Exchange Evaluation, the Vaccine Preparedness Initiative, and the National AIDS Demonstration Research program (NADR).	Syringe Exchange Evaluation study, n=280; Vaccine Preparedness Initiative cohort, n=133 continuing exchangers and n=188 non-exchangers; and the NADR, n=1029.
Donoghoe et al., 1989	Uses a questionnaire to measure changes in sexual behavior among syringe exchange clients over 2–4 months.	142 NSE clients.

Outcome Measures	Results	Limitations
HIV incidence.	HIV incidence among continuing exchange users in the Syringe Exchange Evaluation was 1.58 per 100 person-years at risk (95% CI: 0.54–4.65). Among continuing NSE users in the Vaccine Preparedness Initiative HIV incidence was 1.38 per 100 person-years at risk (95% CI: 0.23–4.57). Incidence among non-users of the exchange in the Vaccine Preparedness Initiative was 5.26 per 100 person-years at risk (95% CI: 2.41, 11.49). In the NADR cities it was 6.23 per 100 person-years at risk (95% CI:4.4, 8.6). Not using an NSE was associated with a hazard ratio of 3.35 (1.29, 8.65) for incidence of HIV infection, compared with using an NSE, in a multivariate proportional hazards analysis.	• Important local conditions that created a strong contrast in the risk for HIV infection between syringe-exchange participants and non-participants. • No causal link between participation in an NSE and lower HIV incidence can be established.
Number of sexual partners; condom use.	Number of participants having no sexual partners increased from 23% to 31%; number having multiple partners decreased from 26% to 21%; and the number having regular partners increased slightly from 49% to 52%. Overall, 79% reported not using condoms.	• Self-reported data. • Reported changes were not significant.

continued

TABLE D-2 Continued

Study	Description	Sample Size (n)
***Gibson et al., 2002**	Compares HIV risk behavior of exchange clients with that of non-clients in San Jose, California, and determines if NSE use is protective against high-risk injection behavior.	212 untreated opiate-addicted IDUs.
Hagan and Thiede, 2000	Studies the influence of the Seattle NSE on sharing of drug injection equipment, to identify potential gaps in risk reduction and to understand in greater detail the lack of an association between exchange use and risk of HBV or HCV transmission.	1,582 IDUs who met eligibility criterion: injecting at least once during the month prior to follow-up.
***Hart et al., 1989**	Monitors the number of clients, visits made, and syringes dispensed and returned at an NSE in London from November 1987 to October 1988.	133 needle exchange clients.

Outcome Measures	Results	Limitations
Frequency of injection; borrowed syringe; borrowed un-sterilized syringe; syringe borrowed only from HIV-negative regular sexual partner; used NSE in past 30 days; got syringes from other sources in past 30 days; injected speedball.	Both univariate and multivariate analysis of the impact of NSE on HIV risk at follow-up revealed a more than two-fold protective effect. In a second multivariate analysis, the odds of HIV risk behavior were decreased more than six-fold for IDUs without other sources of syringes.	• Attrition from baseline to follow-up rendered the sample less representative. • Small sample size. • Grouping of other sources of syringes in the data analysis, since these sources may have been heterogeneous in terms of the risks they pose to IDUs.
Sharing of drug injection equipment (syringes, drug cookers, filtration cotton); NSE use.	In univariate and multivariate analyses, NSE use was associated with a lower likelihood of injection with a used syringe (AOR 0.7; 95% CI: 0.5–0.9). There was no association between NSE use and cooker or cotton sharing, or between NSE use and use of a common syringe to divide drugs.	• Self-reported data. • Large loss to follow-up (but follow-up rate is still high).
HIV infection; injection risk behavior; sexual risk behavior.	The rate of lending and borrowing used injecting equipment fell, both compared with rates before entry to the NSE and during the study. Frequency of injection did not increase and there was reduced incidence of abscesses. There was a reduction in the proportion of clients with multiple sex partners.	• Changes were not significant • Self-reported data. .

continued

TABLE D-2 Continued

Study	Description	Sample Size (n)
***Hartgers et al., 1992**	Studies factors related to regular participation in the Amsterdam syringe exchange and the borrowing of syringes.	131 HIV seronegative IDUs.
Huo et al., 2005	Examines the changes in multi-person use of drug injection paraphernalia during the mid-1990s in Chicago.	794 street-recruited IDUs.

Outcome Measures	Results	Limitations
Frequency of injection; borrowing needles and/or syringes.	29% of the IDUs reported borrowing syringes in the past 4–6 months. Users at increased risk of borrowing were previous borrowers, long-term moderate/heavy alcohol users, current cocaine injectors, and drug users without permanent housing. Regular clients of NSE were found more often to be frequent long-term injectors, and borrowed slightly less often than other users (not statistically significant even after controlling for confounders).	• Sample included only HIV-negative IDUs (those at risk for acquiring HIV). • Self-reported data. • Small sample size.
Five injection equipment sharing practices: receptive sharing, syringe-mediated sharing, and sharing of cookers, cotton filters, or rinse water.	During follow-up the proportion of all sharing behaviors decreased significantly, especially receptive syringe sharing. Participation in an NSE was associated with a one-third decrease in syringe and syringe-mediated sharing, but there was no association with sharing of cookers.	• Convenience sample of IDUs in Chicago. • Significant number of participants were lost to follow-up. • Self-reported data. • Study not designed to evaluate NSE.

continued

TABLE D-2 Continued

Study	Description	Sample Size (n)
***Mansson et al., 2000**	Evaluates the virological efficacy of a needle and syringe exchange program in Malmo, Sweden.	515 IDUs.
Marmor et al., 2000	Develops methods for identifying IDUs with accelerating injection habits, so that they may be referred to counseling and treatment. Investigates behavioral correlates of accelerating injection habits, including NSE use.	328 seronegative IDUs.

Outcome Measures	Results	Limitations
HIV, HBV, HCV seroconversion.	No new HIV infections occurred during a median follow-up of 31 months. Of 159 IDUs negative at baseline for HBV and/or HCV, 35% seroconverted to one or both viruses during follow-up. Multiple logistic regression analysis correlated hepatitis seroconversion with imprisonment during the study (OR 2.2; 95%CI: 1.04–4.74), absence of drug-free periods (OR=5.7; CI: 1.44–22.3), and frequent needle and syringe exchanges (OR=1.31; 95% CI: 1.02–1.7).	• Absence of spread of HIV in this program may have been influenced by other factors such as the low prevalence of HIV infection among IDUs in Southern Sweden. • Many of hepatitis seroconverters report imprisonment during the study.
Drug injection rates (accelerating, decelerating, stable); syringe exchange use (consistent, sporadic, non-user).	All groups of syringe exchange users showed significantly decelerating drug injection. Rates of decline were significantly less among consistent syringe exchange users than sporadic or nonusers of syringe exchanges. 30% of consistent NSE users had accelerating rates of drug injection as compared to 9% of nonusers and 17% of sporadic users.	• Self-reported data. • Possible selection bias.

continued

TABLE D-2 Continued

Study	Description	Sample Size (n)
***Monterroso et al. 2000**	Assesses HIV prevalence and incidence in IDUs and evaluates some of the behaviors and programs street-recruited IDUs employ for HIV prevention.	2,306 IDUs (available at follow-up) in Baltimore, New York, Chicago, San Jose, Los Angeles, and Connecticut (women's correctional facility).
***Ouellet et al., 2004**	Assesses associations between needle exchange program use and drug injection practices in Chicago between 1997 and 2000.	558 regular NSE users (obtained at least half of their needles from an NSE) and 175 IDUs who did not use an NSE.

Outcome Measures	Results	Limitations
HIV-related risk behaviors.	Not using previously used needles was substantially protective against HIV seroconversion (RR=0.29; 95% CI: 0.11–0.80) and in a multivariate model was significantly associated with use of NSEs (AOR=2.08). Reduction of injection frequency was protective against seroconversion (RR=0.33), and this behavior was associated with participation in drug treatment programs (AOR=3.54).	• Problems recruiting and then re-recruiting large numbers of IDUs in several US cities. • High dropout rate.
Frequency in the past 6 months of injecting with a needle used by another person; providing a used needle to another person; backloading; sharing cookers, cotton, or rinse water with others.	In multivariate analysis, regular NSE users, compared with non-users, were less likely to receptively share needles (AOR=0.30; 95% CI: 0.19–0.46); lend used needles (AOR=0.47; 95% CI: 0.31–0.71); share cookers (AOR=0.39; 95% CI: 0.25–0.61); cottons (AOR=0.48; 95% CI: 0.32–0.72); or water (AOR=0.41; 95% CI: 0.27–0.63); or use a needle for > 1 injection (AOR=0.15; 95% CI: 0.08–0.27). Among those who shared needles, regular NSE users were significantly more likely to do so for a smaller proportion of injections, with fewer partners and persons socially closer, and to have always bleached used needles before injecting.	• Possible selection and dilution biases. • Temporal relationship of risk behaviors and NSE use is uncertain. • Sample was not randomly selected. • Self-reported data.

continued

TABLE D-2 Continued

Study	Description	Sample Size (n)
***Safaeian et al., 2002**	Investigates the extent to which differential misreporting of NSE attendance could bias risk estimates. From 1994 to 1997, self reports of NSE attendance from participants in a prospective study in Baltimore were compared with NSE records.	1,315 participants in prospective study.
***Schechter et al., 1999**	Investigates the association between NSE attendance and higher HIV prevalence rates among IDUs in Vancouver to determine whether NSE was causally associated with the spread of HIV.	694 IDU (HIV-negative at recruitment and had injected illicit drugs within the past month).
***Schoenbaum et al., 1996**	Studies injection behavior of IDUs who did and did not utilize a local needle exchange in the Bronx, New York City.	904 IDUs attending a methadone treatment program who injected between 1985 and 1993.

Outcome Measures	Results	Limitations
Self-reports of NSE attendance.	35% had registered with the Baltimore NSE. There was 86.7% concordance between self-reported and actual NSE use; 11% reported NSE attendance but did not attend (over-reported); and 2.2% reported not attending NSE but did attend (under-reported). Persons who over-reported NSE attendance were more likely to have injected frequently, denied needle sharing, and been an HIV seroconverter (AOR=1.83; 95%CI: 1.11–3.01).	• Unlikely to have eliminated misclassification altogether because secondary exchange is common in Baltimore. • Could not pinpoint the exact date when HIV seroconverters became consciously aware of their diagnosis.
Injection risk behaviors, sexual risk behaviors, needle exchange use.	Cumulative HIV incidence was significantly elevated in frequent NSE attendees. Only 1 out of 498 respondents cited the NSE as the site of meeting new sharing partners. There was no increase in risk behaviors among frequent attendees. Frequent attendees were more likely to report: unstable housing, frequent cocaine injection, sex trade involvement, injecting in shooting galleries, and incarceration within the past 6 months.	• Self-reported data. • Vancouver NSE opened several years prior to the initiation of study.
Use of NSE, injection behavior.	21.9% of participants used the NSE. Exchange users shared needles less than non-users ($p<0.05$ in 1993). The HIV seroconversion rate was similar among needle exchange users and non-users (1.77 vs. 1.69 per 100 person-years).	• Sample may not be representative of the population (methadone program clients).

continued

TABLE D-2 Continued

Study	Description	Sample Size (n)
***Strathdee et al., 1997**	Describes prevalence and incidence of HIV-1, HCV and risk behaviors in a cohort of IDUs in Vancouver.	1,006 IDUs who had injected illicit drugs within the previous month recruited from street outreach.
van Ameijden and Coutinho, 1998	Examines whether the decrease in HIV incidence and injecting risk behaviors is ongoing in Amsterdam (1986-1997), and studies the determinants of injecting risk behaviors.	879 IDUs.
van den Hoek et al., 1989	Determines whether drug users are able to change their risk behavior and if risk reduction occurred, whether this can be ascribed to the prevention campaign or to the effect of serological testing and counseling during the study in Amsterdam from 1985 to1988.	263 IDUs.

Outcome Measures	Results	Limitations
Prevalence and incidence of HIV-1 and HCV.	Prevalence rates of HIV-1 and HCV were 23% and 88%, respectively. Estimated HIV incidence was 18.6 per 100 person-years. Independent predictors of HIV-positive serostatus were low education, unstable housing, commercial sex, borrowing needles, being an established IDU, injecting with others, and frequent NSE attendance.	• Estimate of incidence could have been biased upward by selective return for follow-up of those at highest risk of HIV. • No comparison studies of HIV incidence among IDU in Vancouver prior to the introduction of NSE in 1988. • Self-reported data.
HIV incidence; injection risk behaviors.	A large initial (1986–1991) risk reduction occurred concerning borrowing and lending needles, multiple needle use, and frequent injecting. From 1991to 1993 onwards there was no substantial further risk reduction. HIV incidence followed the same trend.	• Due to study design, causal relationships between interventions and outcome cannot be established.
Drug-related risk behaviors.	No increase in the proportion injecting drugs or the frequency of drug use. There was a decrease in sharing of used needles/ syringes. Use of the NSE increased over time.	• Participants may not represent general population of drug users in Amsterdam. • Self-reported data.

continued

TABLE D-2 Continued

Study	Description	Sample Size (n)
van Haastrecht et al., 1996	Evaluates the role of behavioral and other variables, both as risk factors for death from all causes and as risk factors for pre-AIDS mortality in IDUs in Amsterdam.	632 treated and untreated IDUs.
***Vertefeuille et al., 2000**	Determines whether enrollment in an NSE was associated with reduction(s) in high-risk injection practices among HIV seropositive drug users in Baltimore.	112 HIV-positive NSE participants.
***Vlahov et al., 1997**	Determines whether enrollment in the Baltimore NSE was associated with short-term reduction in risky injection practices.	221 NSE participants.

Outcome Measures	Results	Limitations
Mortality.	The study recorded 77 deaths. In IDUs, HIV-positive serostatus, age above 40, and the use of benzodiazepines several times daily were significantly associated with an elevated risk of death, for both death from all causes and death preceding AIDS diagnosis. Daily use of methadone and participation in NSEs were not associated with lower mortality rates.	• Misclassification may have occurred. • Vital status of some participants could not be determined, particularly because of moving out of Amsterdam. • Bias may occur when mortality is associated with censoring. • Mortality may be a poor indicator of HIV risk.
Drug injection practices; location of injection; syringe disposal; and drug use.	Self-reported lending of used syringes to others decreased (34% vs. 15.5%, p=0.001), borrowing of syringes from others decreased (23.2% vs. 11.1%, p=0.002), and reported participation in drug treatment increased (8% vs. 18.8%, p=0.01)	• Lack of external comparison group. • All NSE participants were self selected into NSE. • Self reported data. • Lack of comprehensive utilization statistics for NSE participants.
Drug-related risk.	From baseline, 2-week, and 6-month follow-up visits, significant reductions were reported in use of a previously used syringe (21.6%, 11%, 7.8%, respectively), lending of one's used syringe to a friend (26.7%, 18.4%, 12%, respectively), and several indirect sharing activities.	• No external comparison group. • Self-selected participants. • Self-reported data.

continued

TABLE D-2 Continued

Study	Description	Sample Size (n)
***Wood et al., 2002**	Seeks explanations for high-risk sharing (defined as borrowing a used needle from someone other than the intimate sexual partner in the previous 6 months) among Vancouver IDUs between January 1999 and October 2000.	776 IDUs reporting drug use in the past 6 months.
Wood et al., 2003	Evaluates the risk profile of the population served by the Vancouver Area Network of Drug Users (VANDU) needle exchange, and determines the factors associated with acquiring syringes from VANDU. VANDU is an unsanctioned all-night needle exchange program on a street corner in an IDU-concentrated neighborhood.	587 active IDUs.

*Indicates an article selected by the Committee for relevance or sound study design.

Outcome Measures	Results	Limitations
High-risk needle sharing (defined as borrowing a used needle from someone other than the intimate sexual partner in the previous 6 months).	Logistic regression analysis found that difficulty gaining access to clean needles (AOR= 3.36), bingeing (AOR= 1.82), frequent cocaine injection (AOR=1.76), and male sex (AOR=1.89) were all independently associated with high risk sharing. Being married (AOR=0.49) and acquiring needles exclusively from a NSE (AOR=0.46) were negatively associated with sharing.	• Participants not included in this study had different characteristics than those who were included (single, younger, HIV negative). • Self-reported data.
Use of NSE; drug-related risk behaviors.	165 participants reported using the VANDU exchange. Participants using the VANDU were more likely to frequently inject cocaine, inject in public, and require help injecting. Use of the exchange was also associated with safe syringe disposal.	• Self-reported data. • Study design was unable to allow determination of why the NSE was able to reach the highest risk IDUs.

TABLE D-3 Ecological Studies

Study	Description	Sample Size (n)
Amundsen et al., 2003	Discusses the effectiveness of legal access to needles and syringes versus HIV counseling and testing in Denmark, Norway, and Sweden.	HIV prevention programs for IDUs in Denmark, Norway, and Sweden.
***Des Jarlais et al., 2005a**	Assesses trends in HIV, HCV, and HIV/HCV infection among IDU from 1990 to 2001 in NYC. This time period included a large expansion of syringe exchange (from 250,000 to 3,000,000 syringes exchanged annually).	For HCV testing, n=72 in 1990–1991 and 412 in 2000–2001.
Des Jarlais et al., 2000	Assesses trends in HIV risk behaviors among IDUs in NYC from 1990 to 1997 in a large drug detoxification treatment program (n=2,588) and a research storefront (n=2,701) located in a high drug use area.	5,289 IDUs.

Outcome Measures	Results	Limitations
HIV incidence rates over time (1980–1996).	Results suggest that a high level of HIV counseling and testing might be more effective than legal access to needles and syringes (needle exchange programs). Sweden and Norway have higher levels of HIV counseling and testing and have significantly lower incidence rates of HIV among IDUs than Denmark where there was legal access to needles and syringes and a lower level of counseling and testing.	• Susceptible populations may be smaller than the number of IDUs at each time interval; difficult to compare the sharing of used or non-sterile drug injection equipment between countries. • Lower incidence rates in Sweden and Norway may be caused by other factors than differences in the levels of HIV counseling and testing and legal access to needles/syringes.
HIV and HCV status.	From 1990 to 2001, HIV prevalence declined from 80% to 59% among sero-negative individuals, and from 90% to 63% overall. HCV prevalence declined significantly.	• Participants were IDUs entering detoxification at Beth Israel and do not represent a random sample of IDUs in NYC. • Did not conduct confirmatory testing of HCV-positive individuals. • The expansion of syringe exchange must be considered a natural experiment, not a randomized clinical trial.
Any unsafe sex with casual partner; any unsafe sex with primary partner; any distributive needle sharing; any receptive needle sharing; any sharing at last injection.	The three injection risk behaviors declined significantly over time ($p<0.01$) at each site. Pooled data shows all five risk behaviors declined significantly ($p<0.01$). Participation in NSEs and HIV counseling and testing increased greatly from 1990 to 1997.	• Self-reported data. • Causal relationship between expansion of programs and decline in risk behaviors is not established.

continued

TABLE D-3 Continued

Study	Description	Sample Size (n)
***Des Jarlais et al., 1995**	Describes prevention activities and risk behaviors in five cities (Glasgow, Scotland; Lund, Sweden; Sydney, Australia; Tacoma, Washington; and Toronto, Ontario) where HIV is present in the IDU population, but sero-prevalence has remained less than 5% during at least 5 years.	5 cities.
***Hurley et al., 1997**	Compares changes over time in HIV seroprevalence in IDUs in cities (n=81) worldwide, with (n=29) and without (n=52) NSEs.	81 cities.

Outcome Measures	Results	Limitations
Identification of prevention measures, drug-related risk behaviors.	There were three common prevention components present in all five cities: (1) implementation of prevention activities when HIV seroprevalence was low; (2) provision of sterile injection equipment; and (3) community outreach to IDUs. Moderate levels of risk behavior continued with one-third or more of IDUs reporting recent unsafe injections.	• In the selection of the cities, it is possible that cities conducting sufficient research to determine stable low seroprevalence are more likely to be concerned with HIV infection among IDUs and have implemented some type of prevention program. • Difficulty establishing causal analyses of HIV prevention among IDUs.
HIV seroprevalence.	On average, seroprevalence increased 5–9% per year in the 52 cities without NSEs, and decreased by 5–8% per year in the 29 cities with NSEs. The average annual change in seroprevalence was 11% lower in cities with NSEs (95% CI: -17.6, –3.9; p=0.004).	• Analysis does not take into account the stage of epidemics. • Seroprevalence data were collected according to different protocols in diverse populations. • Cities were selected for analysis by the existence of HIV seroprevalence surveys, and bias may have been introduced by the decision to do a survey. • HIV seroprevalence may have remained low in some of the cities with NSEs, regardless of their introduction. • It was not possible to separate the effects of implementation of NSEs from the other HIV prevention strategies.

continued

TABLE D-3 Continued

Study	Description	Sample Size (n)
***MacDonald et al., 2003**	Uses an ecological study design to determine change in HIV prevalence among IDUs between cities (total n=99) with (n=36) and without (n=63) NSEs.	99 cities.

*Indicates an article selected by the Committee for relevance or sound study design.

Outcome Measures	Results	Limitations
HIV seroprevalence.	HIV prevalence decreased by 18.6% per year in cities that introduced NSEs, and increased by 8.1% in cities that had never introduced NSEs. In cities with an initial HIV prevalence less than 10%, the mean annual weighted increase in HIV prevalence was 32.1% in cities that did not introduce NSEs as compared to a mean annual decrease of 7.8% in cities with NSEs.	• Seroprevalence data used were collected according to different protocols and in diverse populations. • Recruitment through NSEs might provide access to less dependent injectors than those recruited through treatment. • Cities were selected for analysis by the existence of HIV seroprevalence surveys, and bias may have been introduced by the decision to do a survey. • It was not possible to separate the effects of implementation of NSEs from the other HIV prevention strategies. • HIV seroprevalence may have remained low in some of the cities with NSEs, regardless of their introduction.

TABLE D-4 Selected Serial Cross-Sectional Studies

Study	Description	Sample Size (n)
Des Jarlais et al., 2005b	Estimates HIV incidence among IDUs in NYC from 1990 to 2002 to assess the impact of an expansion of syringe exchange services, using the Serologic Testing Algorithm for Recent HIV Seroconversion (STARHS) system.	3,651 IDUs.
Hammett et al., 2006	Evaluation of an intervention (peer education and provision of clean needles through distribution and pharmacy vouchers) in the cross-border region of China and Vietnam.	Surveys conducted prior to the start of the intervention and at 6, 12, 18, and 24 months thereafter.
Van Ameijden et al., 1994	Studies trends in injecting risk behavior from 1986 to 1992 in Amsterdam.	616 IDUs.

Outcome Measures	Results	Limitations
HIV incidence.	HIV incidence declined from 3.55/100 person-years at risk (PYAR) from 1990 to 1992 to 2.63/100 PYAR from 1993 to 1995, to 1.05/100 PYAR from 1996 to 1998, and to 0.77/100 PYAR from 1999 to 2002 ($p<0.001$). There was a strong linear relationship between the annual numbers of syringes exchanged and estimated HIV incidence.	• Limitations of STARHS include: —Need larger sample size to accurately calculate incidence using STARHS. —Potential for false negative HIV results because EIA is less sensitive and may fail to detect antibodies in some cases.
Program coverage of IDUs; IDUs' risk behaviors; HIV prevalence among IDUs during the first 24 months after the intervention was initiated.	Drug-related risk behaviors declined in frequency, and HIV prevalence among IDUs remained stable in China and declined in Vietnam, over the 24 months since the intervention.	• Based on non-random samples of IDUs. • Self-reported data. • Absence of control groups.
Borrowing and lending of injection equipment; reuse of needles and syringes.	Borrowing of injection equipment declined from 51% to 20%; lending of injection equipment declined from 46% to 10%; and reuse of needles and syringes declined from 63% to 39%. Indications were found that voluntary HIV testing led to less borrowing, lending, and reuse of equipment; and obtaining needles via NSE led to less reuse of needles/syringes.	• Participants showing a high level of risk may have been selectively recruited earlier in time. • Selected only drug users who had injected in the preceding 6 months. • Self-reported data. • Outcomes of borrowing and lending are only roughly measured.

continued

TABLE D-4 Continued

Study	Description	Sample Size (n)
Watters et al., 1994	Evaluates an all-volunteer syringe exchange program in San Francisco using 11 semiannual cross-sectional surveys between December 1986 and June 1992.	5,644 IDUs recruited in two 21-day drug detoxification clinics and three street settings.

Outcome Measures	Results	Limitations
Use of syringe exchange program; source of syringes; frequency of injection; initiation into drug injection; frequency of syringe sharing.	In 1992, 45% reported usually obtaining injection equipment from the syringe exchange, and 61% reported using the program within the past year. From December 1986 to June 1992, the median reported frequency of injection declined from 1.9 injections per day to 0.7 injections per day, and the percentage of new initiates into injection drug use decreased from 3% to 1%.	• Self-reported data. • Identifies correlates of sharing syringes, but not causes of reduced sharing. • Targeted samples used were not true random samples.

TABLE D-5 Selected Cross-Sectional Studies

Study	Description	Sample Size (n)
Hagan et al., 1993	Reports on the operation and effectiveness of the first legally operated syringe exchange program in the U.S. in Tacoma, Washington.	204 syringe exchange users.
Keene et al., 1993	Two-year study evaluates specialist- and community-based NSE in Wales from 1990–1991.	152 NSE attenders; 176 non-attenders.
Kerr et al., 2005	Examines factors associated with syringe sharing in a community-recruited cohort of illicit IDUs in a setting where a safer injection facility recently opened.	431 active IDUs.
Klee et al., 1991	Compares three groups of IDUs (on methadone treatment for more than 6 months, on methadone for less than 6 months, no methadone treatment) based on variables believed to be associated with sharing of injecting equipment.	98 IDUs receiving no treatment; 74 IDUs receiving methadone for > 6 months; 44 IDUs receiving methadone for < 6 months.

Outcome Measures	Results	Limitations
Drug use; injection practices; unsafe injections.	Frequency of injection did not change, but the frequency of unsafe injection declined (from 56 to 30 times a month). There was no increase in illicit drug use.	• Retrospective sampling. • Self-reported data. • 28% of potential subjects refused to participate because of the need to relieve withdrawal symptoms.
Syringe sharing in the last year and the last 4 months.	Only 9% of attenders had recently shared syringes in 1990 (10% in 1991) compared with 41% of non-attenders (39% in 1991). 80% of needles and syringes were returned.	• Self reported data. • Comparison of two cross-sectional surveys.
Syringe sharing (borrowing or lending of a used syringe in the past 6 months).	Among participating IDUs, 11.4% reported sharing syringes. In logistic regression analyses, use of the safer injection facility was independently associated with reduced syringe sharing (AOR=0.30; 95% CI: 0.11–0.82; p=0.02), after adjustment for relevant sociodemographic and drug-use characteristics.	• Findings could be due to residual confounding if the SIF had selected IDUs who were inherently at lower risk of syringe sharing. • Not a random sample. • Cannot establish causal relationship because of study design. • Self reported data.
Sharing of injecting equipment; use of NSE.	Regular use of needle exchange was associated with the passing on of used equipment to others.	• Self-reported data. • Sample may not be representative of the population (methadone program clients). • Statistical analysis did not clarify the effect of NSE.

continued

TABLE D-5 Continued

Study	Description	Sample Size (n)
Longshore et al., 2001	Tests frequency of attendance at an NSE in Providence, Rhode Island, as a correlate of injection risk indicators.	248 IDUs.
Vazirian et al., 2005	Compares the risk behaviors of IDUs with differential exposure rates to an HIV outreach program in Tehran, Iran. The outreach program includes a needle and syringe exchange program.	213 IDUs and 85 non-IDUs.

Outcome Measures	Results	Limitations
Sharing of needles, cookers, and cotton filters; cleaning of the skin before injecting; and use of bleach as a needle disinfectant.	Results showed that IDUs who attended the NSE less frequently were more likely to report needle sharing, less likely to report always cleaning their skin, and more likely to report sharing cookers (the NSE distributes cotton and cookers in addition to needles). There was no association between NSE attendance and using bleach as a disinfectant.	• May have underestimated relevance of NSE attendance for skin cleaning. • Self-reported data. • Frequency of NSE attendance is not a sensitive measure. • IDUs were not randomly assigned to the NSE or a non-NSE control group, and NSE attendees were not randomly assigned to various frequencies of attendance.
Contact with outreach program; length of contact; number of syringes received; HIV risk characteristics.	Of those (37) who received few needles/syringes from the program, 18.9% reported using a shared needle or syringe at last injection. None of the 68 IDUs who received >7 syringes per week from the program shared a needle at last injection. There was no difference in the two groups in sharing of cookers, condom use during last sex, level of HIV knowledge, or history of HIV testing.	• Study design does not allow authors to make causal associations. • Selection bias due to convenience sampling. • Self reported data.

REFERENCES

Amundsen EJ, Eskild A, Stigum H, Smith E, Aalen OO. 2003. Legal access to needles and syringes/needle exchange programmes versus HIV counseling and testing to prevent transmission of HIV among intravenous drug users: A comparative study of Denmark, Norway and Sweden. *European Journal of Public Health*. 13(3):252–258.

Bluthenthal RN, Kral AH, Gee L, Erringer EA, Edlin BR. 2000. The effect of syringe exchange use on high-risk injection drug users: A cohort study. *AIDS*. 14(5):605–611.

Bruneau J, Lamothe F, Franco E, Lachance N, Desy M, Soto J, Vincelette J. 1997. High rates of HIV infection among injection drug users participating in needle exchange programs in Montreal: Results of a cohort study. *American Journal of Epidemiology*. 146(12):994–1002.

Bruneau J, Brogly SB, Tyndall MW, Lamothe F, Franco EL. 2004. Intensity of drug injection as a determinant of sustained injection cessation among chronic drug users: The interface with social factors and service utilization. *Addiction*. 99(6):727–737.

Cox GM, Lawless MC, Cassin SP, Geoghegan TW. 2000. Syringe exchanges: A public health response to problem drug use. *Irish Medical Journal*. 93(5):143–146.

Des Jarlais DC, Hagan H, Friedman S, Friedmann P, Goldberg D, Frischer M, Green S, Tunving K, Ljungberg B, Wodak A, Ross M, Purchase D, Millson M, Myers T. 1995. Maintaining low HIV seroprevalence in populations of injecting drug users. *Journal of the American Medical Association*. 274(15):1226–1231.

Des Jarlais DC, Marmor M, Paone D, Titus S, Shi Q, Perlis T, Jose B, Friedman SR. 1996. HIV incidence among injecting drug users in New York City syringe-exchange programmes. *Lancet*. 348(9033):987–991.

Des Jarlais DC, Perlis T, Friedman SR, Chapman T, Kwok J, Rockwell R, Paone D, Milliken J, Monterroso E. 2000. Behavioral risk reduction in a declining HIV epidemic: Injection drug users in New York City, 1990-1997. *American Journal of Public Health*. 90(7): 1112–1116.

Des Jarlais DC, Perlis T, Arasteh K, Torian LV, Hagan H, Beatrice S, Smith L, Wethers J, Milliken J, Mildvan D, Yancovitz S, Friedman SR. 2005a. Reductions in hepatitis C virus and HIV infections among injecting drug users in New York City, 1990-2001. *AIDS*. 19(Suppl 3):S20–S25.

Des Jarlais DC, Perlis T, Arasteh K, Torian LV, Beatrice S, Milliken J, Mildvan D, Yancovitz S, Friedman SR. 2005b. HIV incidence among injection drug users in New York City, 1990 to 2002: Use of serologic test algorithm to assess expansion of HIV prevention services. *American Journal of Public Health*. 95(8):1439–1444.

Donoghoe MC, Stimson GV, Dolan KA. 1989. Sexual behaviour of injecting drug users and associated risks of HIV infection for non-injecting sexual partners. *AIDS Care*. 1(1): 51–58.

Gibson DR, Brand R, Anderson K, Kahn JG, Perales D, Guydish J. 2002. Two- to sixfold decreased odds of HIV risk behavior associated with use of syringe exchange. *Journal of Acquired Immune Deficiency Syndromes*. 31(2):237–242.

Hagan H, Thiede H. 2000. Changes in injection risk behavior associated with participation in the Seattle needle-exchange program. *Journal of Urban Health*. 77(3):369–382.

Hagan H, Des Jarlais DC, Purchase D, Friedman SR, Reid T, Bell TA. 1993. An interview study of participants in the Tacoma, Washington, syringe exchange. *Addiction*. 88(12): 1691–1697.

Hagan H, Des Jarlais DC, Friedman SR, Purchase D, Alter MJ. 1995. Reduced risk of hepatitis B and hepatitis C among injection drug users in the Tacoma syringe exchange program. *American Journal of Public Health*. 85(11):1531–1537.

Hammett TM, Kling R, Johnston P, Liu W, Ngu D, Friedmann P, Binh KT, Dong HV, Van LK, Donghua M, Chen Y, Des Jarlais DC. 2006. HIV prevalence and HIV risk behaviors among injection drug users prior to and 24 months following implementation of cross-border interventions in Northern Vietnam and Southern China. *AIDS Education and Prevention.* 18:97–115.

Hart GJ, Carvell AL, Woodward N, Johnson AM, Williams P, Parry JV. 1989. Evaluation of needle exchange in central London: Behaviour change and anti-HIV status over one year. *AIDS.* 3(5):261–265.

Hartgers C, van Ameijden EJ, van den Hoek JA, Coutinho RA. 1992. Needle sharing and participation in the Amsterdam Syringe Exchange program among HIV-seronegative injecting drug users. *Public Health Reports.* 107(6):675–681.

Huo D, Bailey SL, Garfein RS, Ouellet LJ. 2005. Changes in the sharing of drug injection equipment among street-recruited injection drug users in Chicago, Illinois, 1994-1996. *Substance Use and Misuse.* 40(1):63–76.

Hurley SF, Jolley DJ, Kaldor JM. 1997. Effectiveness of needle-exchange programmes for prevention of HIV infection. *Lancet.* 349(9068):1797–1800.

Keene J, Stimson GV, Jones S, Parry-Langdon N. 1993. Evaluation of syringe-exchange for HIV prevention among injecting drug users in rural and urban areas of Wales. *Addiction.* 88(8):1063–1070.

Kerr T, Tyndall M, Li K, Montaner J, Wood E. 2005. Safer injection facility use and syringe sharing in injection drug users. *Lancet.* 366(9482):316–318.

Klee H, Faugier J, Hayes C, Morris J. 1991. The sharing of injecting equipment among drug users attending prescribing clinics and those using needle-exchanges. *British Journal of Addiction.* 86(2):217–223.

Longshore D, Bluthenthal RN, Stein MD. 2001. Needle exchange program attendance and injection risk in Providence, Rhode Island. *AIDS Education and Prevention.* 13(1): 78–90.

MacDonald M, Law M, Kaldor J, Hales J, Dore GJ. Effectiveness of needle and syringe programmes for preventing HIV transmission. 2003. *International Journal of Drug Policy Sterile Syringe Access for Injection Drug Users in the 21st Century: Progress and Prospects.* 14(5-6):353–357

Mansson AS, Moestrup T, Nordenfelt E, Widell A. 2000. Continued transmission of hepatitis B and C viruses, but no transmission of human immunodeficiency virus among intravenous drug users participating in a syringe/needle exchange program. *Scandinavian Journal of Infectious Diseases.* 32(3):253–258.

Marmor M, Shore RE, Titus S, Chen X, Des Jarlais DC. 2000. Drug injection rates and needle-exchange use in New York City, 1991-1996. *Journal of Urban Health.* 77(3): 359–368.

Monterroso E, Hamburger M, Vlahov D, Des Jarlais DC, Ouellet L, Altice F, Byers R, Kerndt P, Watters J, Bowser B, Fernando MD, Holmberg S. 2000. Prevention of HIV infection in street recruited injection drug users. *Journal of Acquired Immune Deficiency Syndromes.* 25:63–70.

Ouellet L, Huo D, Bailey SL. 2004. HIV risk practices among needle exchange users and nonusers in Chicago. *Journal of Acquired Immune Deficiency Syndromes.* 37(1):1187–1196.

Patrick DM, Strathdee SA, Archibald CP, Ofner M, Craib KJ, Cornelisse PG, Schechter MT, Rekart ML, O'Shaughnessy MV. 1997. Determinants of HIV seroconversion in injection drug users during a period of rising prevalence in Vancouver. *International Journal of STDs and AIDS.* 8(7):437–445.

Safaeian M, Brookmeyer R, Vlahov D, Latkin C, Marx M, Strathdee SA. 2002. Validity of self-reported needle exchange attendance among injection drug users: Implications for program evaluation. *American Journal of Epidemiology*. 155(2):169–175.

Schechter MT, Strathdee SA, Cornelisse PG, Currie S, Patrick DM, Rekart ML, O'Shaughnessy MV. 1999. Do needle exchange programmes increase the spread of HIV among injection drug users?: An investigation of the Vancouver outbreak. *AIDS*. 13(6):F45–F51.

Schoenbaum EE, Hartel DM, Gourevitch MN. 1996. Needle exchange use among a cohort of injecting drug users. *AIDS*. 10(14):1729–1734.

Strathdee SA, Patrick DM, Currie SL, Cornelisse PG, Rekart ML, Montaner JS, Schechter MT, O'Shaughnessy MV. 1997. Needle exchange is not enough: Lessons from the Vancouver injecting drug use study. *AIDS*. 11(8):F59–F65.

van Ameijden EJ, Coutinho RA. 1998. Maximum impact of HIV prevention measures targeted at injecting drug users. *AIDS*. 12(6):625–633.

van Ameijden EJ, van den Hoek JA, van Haastrecht HJ, Coutinho RA. 1992. The harm reduction approach and risk factors for human immunodeficiency virus (HIV) seroconversion in injecting drug users, Amsterdam. *American Journal of Epidemiology*. 136(2):236–243.

van Ameijden EJ, van den Hoek AR, Coutinho RA. 1994. Injecting risk behavior among drug users in Amsterdam, 1986 to 1992, and its relationship to AIDS prevention programs. *American Journal of Public Health*. 84(2):275–281.

van den Hoek JA, van Haastrecht HJ, Coutinho RA. 1989. Risk reduction among intravenous drug users in Amsterdam under the influence of AIDS. *American Journal of Public Health*. 79(10):1355–1357.

van Haastrecht HJ, van Ameijden EJ, van den Hoek JA, Mientjes GH, Bax JS, Coutinho RA. 1996. Predictors of mortality in the Amsterdam cohort of human immunodeficiency virus (HIV)-positive and HIV-negative drug users. *American Journal of Epidemiology*. 143(4):380–391.

Vazirian M, Nassirimanesh B, Zamani S, Ono-Kihara M, Kihara M, Ravari SM, Gouya MM. 2005. Needle and syringe sharing practices of injecting drug users participating in an outreach HIV prevention program in Tehran, Iran: A cross-sectional study. *Harm Reduction Journal*. 2:19.

Vertefeuille J, Marx MA, Tun W, Huettner S, Strathdee SA, Vlahov D. 2000. Decline in self-reported high-risk injection-related behaviors among HIV-seropositive participants in the Baltimore needle exchange program. *AIDS and Behavior*. 4(4):381–388.

Vlahov D, Junge B, Brookmeyer R, Cohn S, Riley E, Armenian H, Beilenson P. 1997. Reductions in high-risk drug use behaviors among participants in the Baltimore needle exchange program. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*. 16(5):400–406.

Watters JK, Estilo MJ, Clark GL, Lorvick J. 1994. Syringe and needle exchange as HIV/AIDS prevention for injection drug users. *Journal of the American Medical Association*. 271(2):115–120.

Wood E, Tyndall MW, Spittal PM, Li K, Hogg RS, Montaner JS, O'Shaughnessy MV, Schechter MT. 2002. Factors associated with persistent high-risk syringe sharing in the presence of an established needle exchange programme. *AIDS*. 16(6):941–943.

Wood E, Kerr T, Spittal PM, Small W, Tyndall MW, O'Shaughnessy MV, Schechter MT. 2003. An external evaluation of a peer-run "unsanctioned" syringe exchange program. *Journal of Urban Health*. 80(3):455–464.

Appendix E

Additional Thoughts on a Community Randomized Trial of Multi-Component HIV Prevention Programs

As discussed in Chapter 3, while evidence shows that the package of services in multi-component prevention programs are effective in reducing drug-related HIV risks, questions remain about the specific contribution of individual elements to reductions in risk behavior and HIV incidence. This issue is important from a policy perspective because certain aspects of the multi-component programs can be resource intensive. Further research is needed to help identify the most effective and cost-effective combination of programs that are feasible to implement in high-risk countries.

One approach for resolving the remaining questions is a multi-national, multi-site trial randomized at the community level (community randomized trial), to evaluate the effectiveness and cost-effectiveness of multi-component programs of increasing complexity. Such a trial could determine whether programs without specific elements are less or possibly more effective and cost-effective, thereby providing policymakers with the tools to make informed decisions about which components to include.

While multiple smaller studies might address some of the questions, such studies might not have sufficient power to demonstrate effectiveness or sufficient sample size to control for confounding effects. Furthermore, because of the difficulty of finding truly single component programs to evaluate in isolation, smaller studies would likely have difficulty disentangling the effects of multiple components in one program.

While not intended to be comprehensive, the following sections provide

an overview of how such a trial might be designed and the operational, logistical, and ethical issues that might arise.

TRIAL DESIGN FEATURES

In a community randomized trial, some communities receive certain added interventions while other communities awaiting such interventions serve as comparison sites (often called "controls"). A stepped-wedge design would be most appropriate for a community randomized trial of multicomponent HIV prevention programs. This design involves sequential rollout of an intervention (whereby intervention components are added to a standard package) in participating communities over time. Areas that are yet to receive a specific intervention serve as controls for the intervention area(s). This design is particularly relevant where an intervention may do more good than harm (making a factorial design, in which certain participants do not receive the intervention, unethical). Such a design is also appropriate where, for logistical, practical, or financial reasons, a program cannot simultaneously deliver an intervention to all participants (Gambia Hepatitis Study Group, 1987).

A community randomized trial makes particular sense for injecting drug users because they may share the same drug-using network and compare their treatment experiences. Thus randomizing participants on an individual basis could create situations where the control group could not be insulated from the intervention group, potentially contaminating the control regimen and blunting the study's ability to detect important differences.

The multi-national, multi-site design feature of the community randomized trial is appropriate for several reasons. First, the burden on individual research sites in implementing a large trial across many communities with sufficient HIV incidence to evaluate interventions is high. Spreading the sample across many sites reduces the burden for a particular research group.

Second, implementing the study at numerous sites allows investigators to evaluate whether the interventions work in different communities. While the interventions would need to be tailored somewhat to the local context, this has proven feasible in trials of similar complexity. The National Institutes of Mental Health (NIMH) Collaborative HIV/STD Prevention Trial is a good example of a multi-national, multi-site community randomized trial. Funded by the National Institutes of Health, the study relies on local public opinion leaders to promote HIV testing and counseling and encourages risk reduction in five developing countries: China, India, Peru, Russia, and Zimbabwe (RTI International, 2005).

Third, using multiple sites increases the statistical power of the study. Because participants within one community are likely to have similar out-

comes, the power of a community trial will be lower than a trial of the same size employing randomization at the individual-level (i.e., the effective sample size will be between the number of participants and the number of sites). Increasing the number of communities will provide more power than increasing the number of participants in a single community. Increasing the number of communities in a single trial does increase logistics and cost, however, and care must be taken to provide adequate resources to enable local partners to carry out the study.

It would be important to select trial sites where the anticipated effect size (percent reduction in the incidence of HIV) would justify the effort. The trial would provide an opportunity to collect data on both biological and behavioral outcomes. One of the limitations of previous evaluations is the reliance on self-reported changes in behavior as a proxy for changes in risk HIV transmission. This study, in contrast, would have the opportunity to measure actual HIV incidence. The trial would also represent an opportunity to evaluate the impact of multi-component prevention programs on HCV transmission. Investigators could consider the feasibility of addressing this primary endpoint during the design phase of the trial.

Secondary outcomes might include subjective and objective measures of risk behavior, including drug-related behavior (such as self-reports of needle sharing and needle disinfection) and sexual behavior (such as self-reports of condom use). Secondary outcomes might also include potential harm at the individual and community level (such as an increase in discarded needles or recruitment of new users). Mediating variables (e.g., self-efficacy in not sharing, or knowledge about infectious disease transmission through sharing of cotton or water) could also be collected. Mediating and moderating variables are important for scrutinizing causal pathways, which distinguish successful interventions from less successful ones. A formative evaluation component could also provide information on the best implementation strategies for the prevention program. Data on program costs and cost-effectiveness could also be collected to help inform decisions on allocating resources.

DESIGN AND IMPLEMENTATION CHALLENGES

A trial of this size and complexity would present major operational and logistical challenges. For example, before the actual trial began, investigators would have to collect baseline measures of biological and behavioral outcomes at all study sites. Investigators would also have to conduct follow-up assessments periodically to measure outcomes. A study of this size would take several years and require extensive cooperation and monitoring among an array of organizations and stakeholders. However, while the proposed rigorous study would present significant challenges, that real-

ity does not obviate the need for it. Experience with the NIMH Collaborative HIV/STD Prevention Trial shows that a trial of this complexity is feasible (Personal communication, D. Celentano, co-principle investigator on NIMH trial, Johns Hopkins University, August 11, 2006).

In approaching such a multi-national and multi-faceted study, critical ethical issues must be anticipated and essential safeguards put in place. Such a trial could be designed in a highly ethical manner consistent with local values. If undertaken, such a study would require extensive and closely coordinated planning and scrupulous attention to the ethical underpinnings. While the details of establishing such assurances and safeguards depend on the specific protocol(s), the basic principles for protecting human rights would apply. Below we outline some of these parameters.

The principles and strategies for ethical safeguards are well identified and can ensure the rights of research participants, as guaranteed under the Declaration of Helsinki and elaborated in the Belmont Accords. All such research must safeguard against exploitation of individuals and communities. Individuals should be afforded the benefits of enhanced treatments (the principle of beneficence), and receive only complementary pre-specified approaches or combinations of approaches whose comparative advantages remain uncertain (the principle of equipoise). Participation in research must be fully informed and freely given according to international and local norms for the particular methodologies being employed, and without repercussion or coercion (respect for dignity and autonomy). Community access to participation should be widely available (distributive justice). For example, extensive promotion of the study would allow as many communities as possible to be considered for participation.

The evaluations would be most informative if conducted in high-risk countries that are initiating programs to protect against HIV among IDUs, given that the evidence base is largely drawn from developed countries. However, the contributions of various components of a comprehensive program are also unknown in countries with more extensive existing HIV prevention programs for IDUs. Thus, communities in these countries might also participate in the trial, furthering the distributive justice of the study.

As noted, a stepped-wedge design would guard against ethical concerns about withholding effective therapies because all communities would eventually receive the interventions. A "no treatment" or "minimal treatment" control arm would be inappropriate. Rather, control communities should have a substantial prevention program equaling or exceeding that already available in the study sites. For example, in evaluating the effectiveness of a needle and syringe exchange component, investigators might provide a basic package of services such as voluntary HIV counseling and testing to promote behavioral change, education on needle disinfection, and referrals to health services and drug treatment in both the control and experimental

communities. Needle and syringe exchange could then be added in the experimental communities.

A multi-national, multi-sector steering committee could help ensure the highest levels of scientific rigor and ethical protection for the trial. Full scientific vetting of protocol(s), informed consent provisions, data quality assurances, periodic review of progress, and transparency of results are requisite for such research integrity. An essential feature of the proposed trial is community involvement in its design and implementation, as well as the development of a community partnership to address concerns prior to and throughout the trial. Plans for sustainability and dissemination of effective interventions are also critical.

TENSION FOR POLICYMAKERS

Policymakers presented with the suggestion for further research confront an inherent tension. On the one hand, there is evidence that multicomponent programs are effective in reducing drug-related risk behavior. As noted in Chapter 3, lack of complete or definitive evidence should not impede implementation of programs vital for protecting public health. On the other hand, this report presents a compelling argument for collecting more evidence, derived from high-risk countries themselves. The policymaking process must be understood as providing ever-greater clarification. A randomized community trial would assure policymakers who are initiating or extending HIV prevention programs that they will learn important lessons, and that they can apply those lessons in a timely and effective way to minimize expenditures and maximize the benefits in their countries.

REFERENCES

Gambia Hepatitis Study Group. 1987. The Gambia Hepatitis Intervention Study. *Cancer Research*. 47:5782–5787.

Research Triangle Institute (RTI) International. 2005. *NIMH Collaborative HIV/STD Prevention Trial Project Overview*. [Online]. Available: http://www.rti.org/u10/overview.cfm [accessed August 22, 2006].

Appendix F

Biographies

COMMITTEE MEMBERS

Hugh Tilson, M.D., DrP.H. (*Chair*), is a Clinical Professor of Public Health Leadership and an Adjunct Professor of Epidemiology and Health Policy at the School of Public Health at the University of North Carolina(UNC). Dr. Tilson received his Doctorate of Medicine (M.D.) from Washington University in St. Louis, Missouri (1964). He is also a Board Certified Specialist in Preventive Medicine and holds both a master's degree and doctoral degree in Public Health from the Harvard School of Public Health (1969–1972). Dr. Tilson is a practicing epidemiologist and outcomes researcher, with a career in preventive medicine and public health spanning more than 40 years. Fifteen years of public service includes duties as a U.S. Army Preventive Medicine Officer in Europe; Consultant to the Federal Office of Economic Opportunity, National Center for Health Services Research, and Veterans Administration; Local Public Health Officer and Human Services Director for Portland, Oregon; and State Public Health Director for North Carolina. Before leaving Oregon for duties in North Carolina, he served as President of the National Association of County Health Officers. He spent 15 years in the multinational pharmaceutical industry for the Wellcome Foundation, latterly GlaxoWellcome. He was founding Co-President of the International Society for Pharmacoepidemiology. In June 1996, he joined the faculty of the UNC School of Public Health. Dr. Tilson currently serves on the faculties of the North Carolina Schools of Medicine, Pharmacy and Public Health, where he is both Clinical and Adjunct Professor. He has

served as Chair of the Clinical Steering Committee for the Pharmaceutical Research and Manufacturers Association (PhRMA). A Fellow of the American College of Epidemiology, and former Vice-Chair of the American Board of Preventive Medicine, Dr. Tilson also served as President of the American College of Preventive Medicine from 1995 to 1997. A founding member of the American Academy of Pharmaceutical Physicians, now the Academy of Pharmaceutical Physicians and Investigators (APPI), he is APPI Vice-President for Policy. Dr. Tilson has served as a member of seven IOM committees, and served as Chair of the Committee on Post-market Surveillance of Pediatric Medical Devices.

Apinun Aramrattana, M.D., Ph.D., is a medical epidemiologist and a leading drug use researcher in Thailand. He is the Deputy Director of the Research Institute of Health Sciences and also the Director of the Northern Substance Abuse Center at Chiang Mai University. Dr. Apinun has been one of the principal researchers who organized the first and second national household surveys of drug use in Thailand in 2001 and 2003. He is the Thailand Principal Investigator on a number of National Institutes of Health (NIH)-supported HIV prevention trials for injection drug users and methamphetamine-using youth, and he is directing a study for the HIV Prevention Trials Network on buprenorphine/naloxone substitution maintenance therapy vs. buprenorphine/naloxone detoxification as an HIV prevention strategy. He also works closely with relevant narcotics control agencies to facilitate policy-relevant research and development projects.

Samuel A. Bozzette, M.D., Ph.D., is Senior Natural Scientist at The RAND Corporation and Adjunct Professor of Medicine (Infectious Diseases) and of International Relations at the University of California (UC) San Diego. He is board-certified in Internal Medicine and Infectious Diseases, and is a Fellow of the American College of Physicians and the Infectious Diseases Society of America. He has a long record of clinical, translational, outcomes, and health economics research, resulting in over 125 scientific publications in universally respected journals and three dozen chapters, reports, and editorials. He headed the Opportunistic Infections and later the Outcomes working groups for the National Institute of Allergy and Infectious Disease's (NIAID's) AIDS Clinical Trials Group and was a leader in the California Collaborative Treatment Group. He has been a Principal Investigator for many large research projects, such as the nationally representative HIV Cost and Services Utilization Study. He founded the Center for Research in Patient-Oriented Care at the Veteran Affairs (VA) San Diego and did seminal work in modeling of potential bioterrorist attacks. Dr. Bozzette is involved in teaching clinical and research skills, and co-directs a training program in Public Policy and Biologic Threats for the

Carnegie Corporation and the UC Institute on Global Conflict and Cooperation. He is a member of the American Society for Clinical Investigation and the Association of American Physicians. Dr. Bozzette holds an M.D. from the University of Rochester and a Ph.D. in Policy Analysis with Distinction in Economics and Quantitative Methods from the Pardee RAND Graduate School of Policy Studies. He has participated in many national, institutional, and civic committees, including an IOM committee on reviewing data needs for the Ryan White Care Act, the VA's National Committee on Clinical Practices Guidelines, and advisory boards for the Zoological Society of San Diego.

David D. Celentano, Sc.D., M.H.S., is a Professor and Director of the Infectious Disease and Epidemiology program and Deputy Chair of the Department of Epidemiology, with joint appointments in the School of Medicine, and International Health and Health, Behavior and Society at the Johns Hopkins University Bloomberg School of Public Health. His research integrates behavioral science theory and research with epidemiology, in the study of infectious diseases. While trained in a chronic disease paradigm (alcoholism and cancer control), he began his research in HIV/AIDS and sexually transmitted diseases (STDs) in the early 1980s. He has worked on some of the major cohort studies (ALIVE, MACS) in HIV epidemiology, as well as conducted intervention research in the United States for heterosexual men and women, injection drug users, and young men who have sex with men. He returned to international research in 1990, when he began a long-term collaboration with Chiang Mai University in northern Thailand. He has worked on and directed numerous HIV/AIDS and STD epidemiological investigations and preventive interventions. More recently, his group has been conducting a prospective study of hormonal contraception in relation to HIV seroconversion, a study with significant family planning policy and health implications. He is currently the Principal Investigator of four NIH-supported studies in Thailand and one in India, focusing on interventions to influence the association between opiate use, methamphetamine use, and other drugs on HIV as well as community-randomized HIV prevention trials. The focus of these interventions is to harness indigenous peer networks for risk reduction. He has over 300 peer-reviewed publications and numerous book chapters. Dr. Celentano has served on two previous IOM studies including the committee reviewing data needs for the Ryan White Care Act and the committee on prevention and control of sexually transmitted diseases.

Mathea Falco, J.D., is the President of Drug Strategies, a nonprofit research institute in Washington, D.C., that identifies more effective approaches to substance abuse. She is also Associate Professor of Public Health at the

Weill Medical College of Cornell University. The author of *The Making of a Drug-Free America: Programs That Work*, Ms. Falco comments frequently on drug policy in the media and in public speeches across the country. Until 1993, she was the Director of Health Policy in the Department of Public Health, Cornell University Medical College in New York City. From 1977 to 1981, Ms. Falco was Assistant Secretary of State for International Narcotics Matters. In earlier positions, she served as Chief Counsel and Staff Director of the U.S. Senate Judiciary Committee, Juvenile Delinquency Subcommittee, and as Special Assistant to the President of the Drug Abuse Council. Ms. Falco is a member of the Council on Foreign Relations and a member of the Board of Directors of the Richard and Rhoda Goldman Fund. She has served on the Board of Overseers of Harvard University, the Board of Trustees of Radcliffe College, and as the Chair of the Visiting Committee on Harvard University Health Services. She has been a member of the national Boards of Directors of Girl Scouts, USA; Big Brothers of America; the International Women's Health Coalition; the Ploughshares Fund; the International Center for Research on Women; the Bridge Fund, and the National Council on Crime and Delinquency. Ms. Falco is a graduate of Radcliffe College and Yale Law School.

Theodore M. Hammett, Ph.D., is a Vice President at Abt Associates Inc., a leading policy research firm with headquarters in Cambridge, Massachusetts. In his 26 years with Abt Associates, Dr. Hammett has focused on HIV/AIDS, particularly in relation to correctional and drug-using populations. Since 2000, he has been principal investigator for a cross-border HIV prevention project for injection drug users, sex workers, and their sexual partners/clients in China and Vietnam, funded by the National Institute on Drug Abuse (NIDA) and the Ford Foundation. Dr. Hammett is also working with Family Health International (FHI) to develop and evaluate interventions to help people being released from drug rehabilitation centers in Vietnam to make healthier transitions to the community. He is a faculty member, focusing on HIV prevention for injection drug users, for an HIV/AIDS policy training program for government officials in China and Vietnam being developed and implemented by the Kennedy School of Government (Harvard University), Tsinghua University (Beijing), and the Ho Chi Minh Political Academy (Hanoi). Dr. Hammett has spoken before numerous national and international conferences, testified before the National Commission on AIDS, and participated in an invited consultation on HIV/AIDS in Prisons at the World Health Organization in Geneva. He has published numerous books, articles, and reports on HIV/AIDS, tuberculosis, and STDs as they affect criminal justice agencies, correctional inmates, and drug-involved populations. In October 2002, Dr. Hammett was

awarded the B. Jaye Anno Award for Excellence in Communication by the National Commission on Correctional Health Care.

Andrei P. Kozlov, Ph.D., graduated in 1972 with a biology degree from St. Petersburg University. From 1972–1975, he completed his postgraduate (Ph.D.) studies at the N.N. Petrov Research Institute of Oncology. In 1978–1979, Dr. Kozlov served in a tenured Research Training Fellowship awarded by the International Agency for Research on Cancer at the laboratory of Robert Gallo at the National Cancer Institute. Currently, he combines several positions: Director of the Biomedical Center, Chairman of an Annual International Conference on "AIDS, Cancer and Public Health," Professor of Biology at St. Petersburg University, and Principal Investigator for a number of international projects. He was among those who discovered first cases of HIV infection in Russia, performed the first isolation of HIV and field studies, described the nascent phase of HIV/AIDS epidemic that took place in Russia in the 1980s and 1990s and transition to concentrated phase, started the first scientifically based preventive programs in HIV/AIDS in Russia, and initiated the Master of Public Health program at St. Petersburg University. Dr. Kozlov also started cohort and preventive studies related to injecting drug users in Russia. Dr. Kozlov is involved in numerous publications which elaborate a national strategy in the field of HIV/AIDS. He was elected a full member of the Russian Medical-Technical Academy. For several years he served as a member of the Advisory Board for the Committee of Science and Education of the Russian Parliament. He won the Russian national Chumakov, Vernadsky, and Mechnikov awards for research in AIDS, immunology, and biotechnology, and the international Paul Harris Fellowship for his contribution in fighting AIDS and other infectious diseases.

Shenghan Lai, M.D., Ph.D., is a Professor of Pathology, Epidemiology, Radiology, and Medicine at the Johns Hopkins School of Medicine, an Adjunct Professor at the Institute of Human Virology, University of Maryland, and a Voluntary Professor at the University of Miami School of Medicine. Before joining Hopkins, he was the Scientific Director of the Comprehensive Drug Research Center, University of Miami School of Medicine. Dr. Lai is recognized as a leading epidemiology researcher in infectious disease epidemiology, and statistical analysis, and world renowned for his research on the effects of HIV infection and cocaine use on subclinical cardiovascular disease, and medical consequences of HIV infection and drug abuse, and international health. Dr. Lai's professional training included medicine, epidemiology, and biostatistics. Dr. Lai received his degrees from Peking Union Medical College in Beijing and the Uniformed

Services University of the Health Sciences in Bethesda, Maryland. He has 140 peer-reviewed publications and numerous book chapters. While trained in medicine and epidemiology, he began his research in HIV/AIDS and STDs in the late 1980s. Dr. Lai has been heavily involved in epidemiology and prevention of HIV infection among IDUs, sex workers, and men who have sex with men for more than 10 years. Dr. Lai is currently the Principal Investigator of four NIH-supported studies in both the United States and China, focusing on HIV natural history and cardiovascular complications of HIV and drug abuse. Dr. Lai is also the Biostatistics Core Leader for Johns Hopkins Reynolds Cardiovascular Research Center.

Ajay Mahal, Ph.D., is an Assistant Professor of International Health Economics at the Department of Population and International Health, Harvard School of Public Health. He has extensive research and policy experience in India, Sri Lanka, Jamaica, Palestine, and elsewhere. His current research interests include the economics of HIV/AIDS, assessing the expenditure implications of aging and changing medical technology in developing countries and ways of integrating human rights concerns into development work. He has written extensively on the economic and human development impacts of the AIDS epidemic, and on the use of policy interventions to address it. In 2002, he worked with a team of professionals at the United Nations Development Programme in New Delhi on a study to assess policy responses to the AIDS epidemic in South Asia, and the emerging lessons for the design of optimal strategies to address HIV in that part of the world. He was most recently the Principal Investigator on a team of Harvard and Nigeria-based researchers to measure the economic impacts of the AIDS epidemic in Nigeria. Dr. Mahal has also served recently as a technical advisor to the Indian National Commission on Macroeconomics and Health (NCMH) in New Delhi that was chaired by the health and finance ministers of India, to develop a long-term strategy for the health sector in India. Prior to his appointment at Harvard, Dr. Mahal was a senior researcher at the National Council of Applied Economic Research in New Delhi, India's premier nongovernment economic research organization. Dr. Mahal has previously served as a resident advisor as part of a health policy advisory team to the Palestinian Authority, based in Gaza, in addition to working on health research and policy-related projects in Sri Lanka, Jamaica, and Nigeria. He has been a consultant to the World Bank, the World Health Organization, the United Nations Development Programme, the Asian Development Bank, the United Nations Conference on Trade and Development, and a number of government and nongovernment organizations. Dr. Mahal holds degrees from Columbia University (Ph.D., 1995) and the University of Delhi (M.A., 1985; B.A. 1983).

Richard S. Schottenfeld, M.D., is a Professor of Psychiatry at Yale University and an experienced clinical researcher who has focused on the efficacy, accessibility, and availability of substance abuse treatments in the United States and abroad. In clinical trials and clinical epidemiologic studies, Dr. Schottenfeld has developed new programs integrating substance abuse treatment with general medical services as well as alternative opioid agonist maintenance programs using medication and behavioral counseling. Current U.S. studies evaluate opioid agonist maintenance treatment in primary medical care settings and novel medications combined with behavioral treatment for heroin and cocaine dependence. Current international studies evaluate the efficacy of naltrexone and buprenorphine treatment with HIV risk reduction and drug abuse counseling for opioid-dependent individuals in Malaysia and Iran. In addition to his Medical School position, Dr. Schottenfeld is the Master of Davenport College (one of Yale's twelve residential colleges).

Suniti Solomon, M.D., is the founder-director of the Y.R. Gaitonde Center for AIDS Research and Education (YRG CARE), a premier HIV/AIDS care and support centre in Chennai, India. She and her colleagues documented the first evidence of the HIV infection in India in 1986. When serving at the Madras Medical College and Government General Hospital as a Professor of Microbiology, she set up the first voluntary testing and counseling centre and an AIDS Research Group in Chennai. Dr. Solomon is a member of the National Technical Team on women and AIDS, a member of the advisory board of International AIDS Vaccine Initiative-India, a member of the Scientific Committee of the National AIDS Research Institute, Pune, Government of India, a permanent member on the Microbicides Committee of the Indian Council for Medical Research (ICMR), a member on the board of AVAHAN, the India HIV/AIDS Initiative of the Bill & Melinda Gates Foundation, a Trustee At-Large of the International Association of Physicians in AIDS Care, and a member of the Asia Data Safety Monitoring Board of the Division of AIDS, NIH, U.S.. Dr. Solomon is the Indian Principal Investigator of several pioneering HIV research studies: the U.S. National Institute of Mental Health's multi-country HIV/STD Prevention Trial; the U.S. National Institute of Allergy and Infectious Diseases' HIV Prevention Trial Networks; an NIH award that will measure stigma in health care settings in Southern India; and a Phase III study of 6 percent CS GEL, a candidate microbicide of CONRAD. She is the Director of the Southern India program of the Brown-Tufts Fogarty AIDS Training and Research Project. Dr. Solomon's experience covers a wide range of aspects related to HIV infection, from biomedical to socio-economic. She has deep interest in community education and mobilization and leads an effort that supports a Phase I HIV vaccine trial at Chennai with community education

and volunteer enrollment. She received a Lifetime Achievement Award for her work with AIDS from the State Government's Medical University in December 2001 and a second Lifetime Achievement Award in 2005 from the Tamil Nadu State AIDS Control Society. Dr. Solomon has published extensively on HIV epidemiology, prevention, care and support, biomedical research, research ethics, and gender issues. She holds an M.D. in microbiology from Madras University. She has trained in pathology in the United Kingdom and the United States. Dr. Solomon currently serves as the President of the AIDS Society of India.

IOM STAFF

Patrick W. Kelley, M.D., DrP.H., joined the Institute of Medicine in July 2003, serving as the Director of the Board on Global Health and the Board on African Academy Science Development. Previously he served in the U.S. Army for more than 23 years as a physician, residency director, epidemiologist, and program manager. In his last Department of Defense (DoD) position, Dr. Kelley founded and directed the Presidentially mandated DoD Global Emerging Infections Surveillance and Response System (DoD-GEIS). This responsibility entailed managing approximately $42 million dollars of emerging infections surveillance, response, training, and capacity-building activities undertaken in partnership with numerous elements of the federal government and with health ministries in over 45 developing countries. He also designed and established the DoD Accessions Medical Standards Analysis and Research Activity, the first systematic DoD effort to apply epidemiology to the evidence-based development and evaluation of physical and psychological accession standards. Dr. Kelley is an experienced communicator, having lectured in over 20 countries and authored over 50 scholarly papers and book chapters. He also designed and served as the specialty editor for the two volume textbook entitled: *Military Preventive Medicine: Mobilization and Deployment*. Dr. Kelley obtained his M.D. from the University of Virginia and his DrP.H. from the Johns Hopkins School of Hygiene and Public Health.

Alicia R. Gable, M.P.H., is a Senior Program Officer with the Board on Global Health. She joined the IOM in 1999 and has served as Study Director on several domestic and international HIV policy studies, including *Measuring What Matters: Allocation, Planning, and Quality Assessment for the Ryan White CARE Act* and *Review of the HIVNET 012 Perinatal HIV Prevention Study*. She also served as a staff officer on three major IOM reports related to the safety of childhood vaccines and on the President's Emergency Plan for AIDS Relief evaluation study. Prior to joining the IOM, Ms. Gable completed a fellowship in health systems adminis-

tration at the Washington Hospital Center in Washington, D.C. She also worked as an economist at Research Triangle Institute and Triangle Economic Research in North Carolina, where she designed and conducted health valuation surveys and natural resource damage assessments. Ms. Gable completed her undergraduate studies at the University of North Carolina at Chapel Hill and her Master of Public Health in health management and policy at the University of Michigan at Ann Arbor.

Alyson Schwaber, M.P.H., is currently a Senior Program Associate working on the study on the Prevention of HIV Infection among Injecting Drug Users in High-Risk Countries. Ms. Schwaber joined the IOM in November 2004 as a Research Associate for the study, *Options for Overseas Placement of U.S. Health Professionals*. Prior to joining the National Academies, Ms. Schwaber was a program manager of sustainable development focused on Africa at Sister Cities International in Washington, D.C. She served as a Peace Corps volunteer in community health in Mauritania from 1999–2001. Following her service, she remained in Mauritania for 2 additional years to work with an HIV/AIDS prevention and education project of an international non-governmental organization. Ms. Schwaber completed her undergraduate studies at Penn State University and her Master of Public Health at Johns Hopkins Bloomberg School of Public Health.

Sheyi Lawoyin, M.P.H., joined the Institute of Medicine in September 2004 and most recently provided support to the Board on Global Health's study on *HIV Prevention among Injecting Drug Users in High-Risk Countries*. Prior to this, she served as a Senior Program Assistant with the Board on Population Health and Public Health Practice in conjunction with the Board on Global Health. In this capacity, she assisted with providing support for the studies on *Reducing Tobacco Use* and *CDC Quarantine Station Expansion Plans at U.S. Ports of Entry*. Ms. Lawoyin recently completed her Master of Public Health degree at the George Washington University's School of Public Health and Health Services with a concentration in Health Policy. Her area of concentration included research in global health policy issues in the areas of HIV/AIDS, malaria and global development. During her graduate studies, she completed an internship with the U.S. Department of State, working at the U.S. Consulate General in Lagos, Nigeria. Her work included conceptualizing, planning and implementing HIV/AIDS educational awareness workshops for young women between the ages of 18–30.