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Drug Abuse Treatment as AIDS Prevention

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SYNOPSIS

Objective. As the acquired immunodeficiency syndrome (AIDS) epidemic among drug users enters its third decade in the United States, it is important to consider the role played by substance abuse treatment in the prevention of human immunodeficiency virus (HIV) infection.

Methods. The authors review the research literature, examining findings from studies with behavioral and serologic measures on the association among treatment participation, HIV risk reduction, and HIV infection.

Results. Numerous studies have now documented that significantly lower rates of drug use and related risk behaviors are practiced by injecting drug users (IDUs) who are in treatment. Importantly, these behavioral differences, based primarily on self-report, are consistent with studies that have examined HIV seroprevalence and seroincidence among drug users.

Conclusion. The underlying mechanism of action suggested by the collective findings of the available literature is rather simple—individuals who enter and remain in treatment reduce their drug use, which leads to fewer instances of drug-related risk behavior. This lower rate of exposure results in fewer infections with HIV. The protective effects of treatment, however, can only be achieved when programs are accessible and responsive to the changing needs of drug users. Future research needs to be directed at developing a better understanding of the factors that enhance treatment entry and retention.

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Since the acquired immunodeficiency syndrome (AIDS) epidemic among injecting drug users (IDUs) was first recognized in the early 1980s, a variety of prevention interventions have been implemented.[1–3] These interventions have included educating drug users about how the human immunodeficiency virus (HIV) is transmitted and ways injectors can prevent infection. Along with educational messages, many prevention initiatives have included the distribution of condoms and bleach and, to a lesser extent, sterile syringes. To deliver these messages and supplies to individuals who are at greatest risk, a major prevention initiative has involved outreach to drug users who are not in treatment. No HIV preventive intervention, however, has been as widely endorsed, or as frequently evaluated, as substance abuse treatment.[4–7]

Treatment is typically not considered prevention; it is usually applied when prevention has failed. However, the close association between drug use and HIV transmission suggests that the treatment of drug abuse can be considered primary HIV prevention. By helping drug users to reduce their frequency of use, participation in substance abuse treatment has been associated with the prevention of HIV infection.[8–10] Given the hidden nature of drug use and its social stigmatization, substance abuse treatment programs are one of the few social institutions that actively seek out and maintain involvement with drug users. Thus, treatment programs provide a location for the delivery and evaluation of HIV prevention interventions. In fact, many of the early efforts directed at understanding the scope of the HIV epidemic and monitoring its spread among drug users were based in treatment programs.[11–13]

To understand the potential of drug treatment as primary prevention, it is necessary to consider the way in which the virus is transmitted among IDUs. Drug use leads to the transmission of HIV and other blood-borne pathogens via direct and indirect routes. Needle sharing, a direct method of transmission, involves the reuse of a contaminated syringe. Infection occurs when blood containing virus from an infected individual remains in a needle or syringe and is injected along with the drug solution into an uninfected user. Drug-related transmission of HIV also may occur when injection paraphernalia other than needles and syringes are reused. These "indirect" methods include using contaminated water to rinse a syringe or mix a drug solution. Similarly, HIV can be transferred via the cooker used to heat and dissolve the drug or the cotton used to strain the drug solution as it is drawn into the syringe.[14] HIV also can be transmitted when injectors, who often pool money to buy drugs, divide the drug solution by using one syringe to fill others. Since the drug can be more accurately divided in its liquid form, using a syringe facilitates fair division and distribution. This practice, known as "frontloading" or "backloading," depending on which end of the syringe is removed, can result in the transfer of infected blood from the syringe used to distribute the solution.[15]

Both direct and indirect methods of viral transmission can occur at the time of injection. Thus, by assisting drug users to effectively eliminate or reduce the frequency of injection, substance abuse treatment can have a primary prevention impact on both direct and indirect risks of HIV infection.

In considering the ability of drug abuse treatment to prevent HIV infection, it is important to note the great variability among treatment programs. The treatment modality most often used by drug injectors is methadone maintenance, a reflection of the large numbers of drug injectors who use heroin alone or in combination with cocaine. Other modalities include outpatient drug-free programs, residential treatment facilities, and therapeutic communities. Treatment philosophies and practices vary across and within these different modalities. Treatment programs also vary with respect to effectiveness.[5]

Similarly, it is common for policy makers and researchers to refer to drug users as being "in treatment" or "out of treatment." The classification does not adequately reflect unstable and sometimes sporadic involvement in treatment over time. When patterns of treatment participation are examined, only a minority of users remain in what might be termed stable patterns of treatment. Most individuals who enter treatment leave within six months, and long-term stable treatment is relatively rare.[5,13,14,16]

Keeping in mind the diversity of substance abuse treatments and the various ways that treatments are implemented and utilized, the underlying mechanism of HIV protection as supported by available data is rather simple. Individuals who "enter" effective treatments reduce their drug use. Lower rates of use lead to fewer instances of drug-related risk behaviors. In turn, lower rates of drug-related risk behaviors result in fewer exposures to HIV and, thus, fewer incident cases. In this model, the individual's use of substances is the causal factor in a chain of events that culminates in infection with HIV. Effective treatments break this chain by reducing the frequency of drug use.

This chapter reviews the research findings that have examined the relationship between treatment participation and HIV risk reduction. In exploring this relationship, two broad research approaches have been used.

First, a number of studies have examined the self-reported frequency of drug use and related risk behaviors among drug users in-treatment and out-of-treatment. Second, a number of studies have reported on the incidence and prevalence of HIV infection among drug users in an effort to understand the protective effects of treatment. Since it would be unethical to withhold drug treatment to test its impact, there have been no randomized controlled clinical trials comparing treatment and no-treatment conditions. Thus, the evidence of the power of treatment must be derived from a broad range of studies that have necessarily used less than ideal methods.

It also should be noted that most of the published research has evaluated the impact of methadone treatment, a modality that serves opiate-dependent drug users. During the first 15 years of the AIDS epidemic, the majority of injectors at risk of HIV infection injected heroin. As a consequence, most studies have focused on this group of users and on methadone treatment. A few studies are beginning to emerge that have evaluated the sexual risk reduction impacts of treatments for noninjecting drug use, behaviors that may well define the future of the epidemic among drug users.

Treatment Involvement and Reduction in Frequency of Injection

The association between treatment participation and reductions in drug use frequency has been repeatedly reported in the literature.[8–10] Perhaps the most consistent finding has been the association between participation in methadone treatment and lower rates of injection.

Nowhere is this association more clearly articulated than in the data from a three-year study that examined the drug use patterns of 633 male IDUs participating in methadone maintenance.[17,18] Study participants were drawn from the active caseloads and the intake rosters of six methadone maintenance treatment programs in New York City, Philadelphia, and Baltimore. All subjects completed a baseline interview and 506 completed a follow-up interview one year later. The results of these interviews allowed investigators to document a clear pattern of drug use in which nearly all subjects reported daily injection prior to treatment entry. Following treatment entry, rapid reductions in injection frequency were observed and continued for those who remained in-treatment. Thirty-seven percent of these subjects reported their last injection occurred just prior to, or during, their time of entry into the program. It is important to note that, for most subjects, the cessation of injection was not immediate upon treatment entry. Similarly, some subjects never ceased injecting while in treatment. Of those interviewed at follow-up, 29% reported injecting an average of 11 days during the month prior to the interview. While drug use was not eliminated completely, when compared to the pretreatment levels of use, the impact of treatment was dramatic: 71% of the subjects had no injections during the prior month, and 60% had no injections during the prior year. Equally dramatic was the rapid return to injecting drug use during the year following treatment. Among those who left treatment, more than 80% injected during the following year.

A similar pattern of reduction in drug use following treatment entry has been reported more recently in analyses of data from drug users recruited in 15 cities as part of the National Institute on Drug Abuse (NIDA) Cooperative Agreement studies.[19] These analyses included 2973 drug users who had been recruited while they were out-of-treatment and followed six months later. Once enrolled, all subjects were randomly assigned to either a standard intervention, which consisted of comprehensive risk reduction counseling and HIV testing delivered in two sessions, or an enhanced intervention, which provided additional risk reduction counseling and referral. During the six-month follow-up interval, 250 (8.4%) had entered and remained in treatment for at least 90 days. Of these, 60% received methadone treatment, 28% received outpatient drug-free treatment, and 29% received residential treatment (approximately 20% had been in multiple treatment programs). When the drug use patterns of these treated subjects were compared with those who had not entered treatment, significantly lower rates of use were seen. Compared with the untreated subjects, those who had entered treatment had injected heroin, cocaine, and speedball (mixture of cocaine and heroin) at significantly lower rates. Also found were significantly lower rates of crack smoking. In addition, individuals who had been in-treatment for 90 days or more were three times more likely to report no drug use at all and nearly four times more likely to provide a urine specimen with no detectable drugs.

Treatment participation also has been associated with reductions in needle sharing. In a large, community-based survey conducted by Caplehorn and Ross, 1200 IDUs from Sydney, Australia, were interviewed regarding their injection practices and treatment participation.[20] Analyses of these data revealed two important findings. First, IDUs in methadone treatment were 50% less likely to report sharing a syringe. Second, and perhaps more importantly, the protective effects of treatment disappeared when individuals who had stopped injecting were removed from

the analyses. Those who were in treatment and continuing to inject were as likely to report needle sharing as those who were out of treatment. These data not only document the lower rates of risk behavior among IDUs in treatment, but also suggest that it is the reduction in drug use that accounts for the protective effects of treatment.

Caplehorn and Ross also summarized the results of eight other studies in which needle sharing among IDUs in methadone treatment was compared with their untreated counterparts from the same communities. These studies were conducted in Australia, Europe, and the United States between 1985 and 1995. With one exception, each study observed significantly lower rates of needle sharing among those in methadone treatment. Rates were from one-third to one-half of the rates found among the out-of-treatment subjects.

Lower rates of risk behaviors among drug users in treatment have been reported by others, and the consistency of their results is notable. Abdul-Quader and associates[21] found that both frequency of drug injecting and injecting in shooting galleries (a common practice early in the epidemic and associated with increased risk of HIV infection) were significantly reduced proportionate to the amount of time spent in methadone maintenance treatment. In a study conducted in New Haven, Connecticut, 107 methadone-maintained IDUs and 314 out-of-treatment IDUs were surveyed regarding their risk behaviors. Frequency of injections was found to be 50% to 65% higher ($P < 0.001$) among the out-of-treatment subjects.[22]

Although this discussion is focused primarily on injecting drug use, data are emerging from the treatment of noninjecting drug use (for example, crack smoking and alcohol), which suggest a strong association between treatment participation and reductions in risky sexual behaviors.

A study of HIV risk behavior change among individuals receiving alcohol treatment was reported by Avins and colleagues.[23] In this study, 700 alcohol-dependent subjects completed a baseline assessment and a follow-up assessment an average of 13 months later. In comparing baseline and follow-up data, significant reductions in both sexual and drug-related risks were found: 58% reduction in injecting drug use, 15% reduction in reports of multiple sex partners, 26% reduction in the number of partners who were IDUs, and 77% increase in the use of condoms with all secondary sexual partners.

In a similarly designed study, Shoptaw and colleagues in Los Angeles[24] found significant reductions in risk behaviors among 232 cocaine-abusing or cocaine-dependent individuals who received up to six months of weekly drug counseling. Despite the fact that no formal HIV prevention interventions were delivered, individuals who completed treatment showed significant decreases in sexual risk behavior, primarily the result of a reduction in the number of sexual partners. Among those who demonstrated a treatment effect, the sexual risk reductions accompanied reductions in cocaine use as monitored by urinalysis.

Together, these data suggest that reductions in injecting and noninjecting drug use often occur following treatment entry and, in turn, HIV risk behaviors become less frequent. While such findings are very encouraging, they are by no means definitive, and they raise important questions about the causal mechanisms responsible for these changes. It also is important to note that all of these findings are based on self-report. Although the self-report of drug-using individuals has often been shown to have acceptable levels of validity and reliability, the behaviors that can transmit HIV are particularly sensitive, making it difficult for participants to disclose them and for researchers to confirm them.[25–27] The only biological marker available for evaluating the potential of substance abuse treatment to prevent HIV infection is HIV infection itself, and a number of studies have examined the relationship between treatment participation and HIV prevalence and incidence.

HIV Prevalence, Incidence, and Participation in Drug Abuse Treatment

A variety of observational methods and nonrandomized research designs have been used to examine prevalence and incidence of HIV infection among IDUs and its relationship to participation in substance abuse treatment. An early report linking treatment participation to lower rates of HIV infection appeared in 1984, shortly after the virus had been isolated and antibody testing became available.[28] In describing prevalence rates among individuals from known risk groups, antibody test results of 86 "heavy intravenous drug users" in New York City found 75 (87%) to be infected, while antibodies to HIV were found in fewer than 10% ($n = 3$) of the samples from 35 methadone patients. All of the methadone patients had been in-treatment for more than three years and according to the authors had "greatly reduced" their injecting drug use.

In 1985, Novick and colleagues reported on the findings of HIV testing from stored samples of blood that had been collected between 1978 and 1983 from IDUs participating in a study of chronic liver disease.[29] Of the 48 subjects who were in methadone treatment at the time

they were studied, 23% (n = 11) tested positive for HIV. The HIV prevalence rate was found to be 17% (n = 6) among those who had been in treatment for five years or longer. Of those not in treatment at the time of study, 47% (n = 25) tested positive for HIV.

In 1988, Brown and associates noted that rates of HIV infection varied with length of time in treatment.[30] Among the 360 injectors studied, those who had been in treatment for longer periods of time had significantly lower rates of infection. Patients who had been in treatment for less than one year were 1.5 times more likely to test positive for HIV than those in treatment for longer than one year. While overall the rate of infection was highest among African American subjects, the relationship between prevalence and duration of treatment was consistent across racial groups.

Together, data from these early prevalence studies suggested that stable methadone treatment was a valuable intervention in preventing HIV infection among IDUs. By the end of the 1980s, several studies had reported on low rates of HIV infection among individuals who had continually been in methadone treatment during the period of rapid spread of HIV infection in their respective communities. For example, in 1988 in New York City, 58 individuals who had been in methadone treatment for an average of 17 years were tested and found to be uninfected with HIV. During the time they had been treated, the prevalence of HIV infection among IDUs in New York had risen to more than 50%.[31] Similarly, Blix and Gronbladh examined HIV testing data collected in 1984 from methadone patients in Uppsala, Sweden.[32] During the time of this study, HIV prevalence rates among IDUs had risen to 38%. Yet, only two infections (3%) were found among 67 patients who had been admitted to methadone treatment prior to 1979. Importantly, these infected individuals were both women in relationships with IDU men. As of 1990, the 65 HIV-negative patients, all of whom had stayed in treatment, remained uninfected.

In an observational study of HIV seroincidence among 681 IDUs, Moss and colleagues examined the characteristics that best distinguished individuals who seroconverted from those who remained uninfected.[33] Subjects in this study were methadone patients who had been tested at least twice while in treatment in San Francisco between 1985 and 1990. The study identified 22 seroconverters for an average annual seroconversion rate of 1.9%. The risk factors found to be significantly associated with seroconversion included having more than five sexual partners per year, ever using a shooting gallery, and having less than one year of methadone maintenance treatment. In fact, more than three times the rate of infection was found among individuals with less than one year of treatment when they were compared with those with a year or more of methadone maintenance treatment.

Consistent with these findings, a prospective seroincidence study of methadone patients in New Haven, Connecticut, identified substantially lower rates of)new infections among subjects with continuous treatment experiences.[34] An overall incidence rate of 2.8 per 100 person-years was found among 98 current and former methadone patients. Among the 56 subjects with continuous treatment, one subject became infected (0.7 per 100 person-years); among the 42 subjects with interrupted treatment, eight became infected (4.3 per 100 person-years). While these findings were consistent with prior studies, given the small sample size and the differential follow-up among the two groups, these differences were not significant.

In a case-control study nested within a prospective evaluation of 952 seronegative IDUs, 40 incident cases were matched to 40 subjects who remained seronegative.[35] In analyses directed at identifying differences between cases and controls, duration of methadone treatment and methadone dosage were found to have dramatic protective effects. For every three months spent out of treatment, the risk of becoming infected with HIV increased by 70%. Further, the higher the methadone dosage, the lower the risk of infection. In multivariate analyses, these variables remained the most salient characteristics in explaining differences between cases and controls.

In Philadelphia, Pennsylvania, a prospective longitudinal study of HIV infection and risk behaviors among in-treatment and out-of-treatment drug users was initiated in 1989.[36] In this study, 152 IDUs were randomly selected from a methadone treatment program and 103 out-of-treatment IDUs were recruited using a chain referral technique. Consistent with prior work, this study found significantly lower rates of needle sharing, injection frequency, shooting gallery use, and visits to crack houses among the methadone-maintained IDUs.

At entry into this study, 18% of the out-of-treatment subjects and 11% of the methadone-maintained clients tested positive for antibodies to HIV. After 18 months of study, 33% of the out-of-treatment cohort were infected compared to 15% of the methadone patients ($P < 0.01$). The incidence of new infection was strongly associated with participation in methadone treatment. When incidence rates were examined in relation to whether or not the subjects remained in treatment, changed their treatment status, or remained out of treatment, dramatically

different rates of incident HIV cases were observed. Individuals who remained out-of-treatment were nearly six times more likely to have become infected than were those who remained in-treatment during the first 18 months of the study. Among those who remained in methadone treatment for the entire 18-month study period, 3.5% became infected with HIV; among those who remained out-of-treatment, 22% became infected with HIV.

Friedman and colleagues reported the results of analyses directed at examining the factors associated with seroconversion among 6882 IDUs who had at least two HIV tests.[37] Subjects were participants in the National AIDS Demonstration Research Projects and the AIDS Targeted Outreach Models projects and were drawn from 15 cities characterized as either high prevalence (>20%) or low prevalence (<8%), based on baseline infection rates. Having been in any drug treatment program during the follow-up interval was the only variable significantly "protective," and it was the only variable that reached significance in both high- and low-prevalence cities.

Discussion

As reviewed in this chapter, many studies have now documented that significantly lower rates of risk behaviors are practiced by drug users who are in treatment. This has been the finding when treated drug users were compared with untreated drug users, when drug use patterns during treatment were compared with pretreatment patterns, and when drug use patterns during treatment were compared with posttreatment drug use practices (see Table 1). Importantly, these self-reported behavioral differences are consistent with seroprevalence and seroincidence data (see Table 2).

One of the consistent findings of both behavioral and serologic studies reported here is the association between duration of treatment and protection from HIV infection. Collectively, these studies suggest that retention in treatment (not merely entry) is associated with protection. In fact, there is some evidence that unstable patterns of treatment are associated with elevated risk. Greater protection is afforded by longer treatment episodes, a conclusion that is consistent with treatment evaluation research that has documented a strong correlation between retention in treatment and effectiveness in reducing drug use.[5]

As one of the few organized social institutions with access to drug users at risk of HIV infection, treatment programs have in many ways become community-based staging areas for risk reduction interventions directed at drug users. A frequently cited concern about using treatment programs as HIV prevention delivery vehicles is that only a minority of drug users are in treatment. It is estimated that 10% to 20% of IDUs are in treatment at any given time.[38] However, treated drug users often remain enmeshed in social networks of those who continue to use drugs and, as such, represent a link to individuals in the community who are not in treatment. Given the typically brief treatment episodes of drug users, most individuals who received interventions while in-treatment will leave and may carry the prevention messages and treatment experiences with them when they return to the community.[39] Thus, by working with IDUs who are in-treatment, it is possible to impact the injecting practices of those drug users who are out-of-treatment.

Unfortunately, funding for substance abuse treatment programs has eroded during the course of the AIDS epidemic; there are now fewer treatment programs available and, within programs, fewer services.[40] Residential services have been particularly affected, and detoxification program regimens now typically extend only a few days. Thus, to maximize the preventive potential of drug and alcohol treat-ment, it will be necessary first to establish funding mechanisms that allow for an expansion of the treatment system and then to provide a stable base for program operations.

The strength of the data presented here derives its power from the consistency of findings among behavioral studies and studies that have used HIV infection as a biological marker of program effectiveness. Yet, one cannot escape the dilemma that, without randomized controlled clinical trials, the lower rates of drug use, risk behavior, and infection cannot be attributed unequivocally to the treatment process.

The most serious threat to the validity of these findings is the possibility of selection bias. It could be argued that individuals who seek and enter drug treatment are, by nature, more likely to practice safer behaviors than those who do not. The available data, however, do not provide strong support for such an interpretation. The findings presented here indicate that both pre- and posttreatment drug use behaviors are dramatically elevated with drug use and related risk behaviors during treatment. Investigators also have identified a dose-response relationship among treatment duration, intensity, and methadone dosage and participation in risk behavior.[41,42] Thus, while methodological challenges may serve a useful purpose in encouraging more rigorous research, they should not prevent us from forming well-reasoned conclusions based on the preponderance of evidence.

Table 1. Summary of studies of risk behaviors and treatment participation

Investigator	*Year*	*Subjects*	*Design*	*Findings*
Abdul-Quader et al.	1987	230 methadone patients from New York City clinic	Retrospective survey	Significant association between time in treatment and reduced rates of drug injection, injection in shooting galleries, and needle sharing.
Ball et al.	1988	633 male methadone patients from six clinics in three cities	Retrospective survey and prospective follow-up	Significantly lower rates of injections during methadone treatment when compared to pre- and posttreatment behaviors.
Meandzija et al.	1994	107 methadone patients and 314 out-of-treatment IDUs in New Haven, CT	Survey	50-65% higher frequency of injection among IDUs not in treatment.
Caplehorn and Ross	1995	1200 IDUs from Sydney, Australia	Survey and meta-analysis of nine studies	Subjects in methadone treatment were 50% less likely to report sharing attributable primarily to reductions in injection; in meta-analysis, eight of nine studies found significantly lower rates of needle sharing among methadone patients when compared with injectors not in methadone treatment.
Booth et al.	1996	250 IDUs who entered treatment from cohort of 2973 recruited in 15 US cities while out of treatment	Observational	Those who entered treatment and remained for 90 days or longer had significantly lower rates of heroin, cocaine, and speedball injection; also significantly lower rates of crack smoking and positive urinalysis at follow-up.
Avins et al.	1997	700 alcohol-dependent subjects in alcohol treatment in San Francisco, CA	Observational with an average of 13-month follow-up	For subjects completing follow-up, 58% reduction in drug injection, 15% reduction in multiple sex partners, and 77% increase in condom use with secondary partners reported.
Shoptaw et al.	1997	232 cocaine-abusing subjects in outpatient treatment	Observational study	Subjects completing treatment reported significantly fewer sex partners.

The data presented here do not address some of the fundamental issues involved in understanding the causal mechanisms of treatment's impact. Clearly, further research is needed in all modalities to investigate the "active ingredients" of substance abuse treatment. At the same time, given the positive findings regarding the effectiveness of treatment, there is a need to increase attention on those factors associated with treatment entry and retention. If treatment programs are to maximize their impact, access is essential. However, very few investigators have carefully examined the factors that attract users into treatment and the barriers that impede treatment entry and retention.[43] Research initiatives need to address treatment access and retention, including drug users' perceptions of drug treatment and the role of treatment in their lives.

The data from the past 20 years suggest that treatment is important but, by itself, insufficient to protect the health of the drug-using community. Not all users are interested in treatment, able to gain access to treatment, or able to remain in treatment, and not all individuals who enter treatment eliminate their use of drugs. HIV prevention will therefore necessarily require the integration of treatment with outreach and harm reduction strategies to help protect the health of drug users and the larger community.

Table 2. Summary of studies of HIV prevalence and incidence and treatment participation

Investigator	*Year*	*Subjects*	*Design*	*Findings*
CDC	1984	86 out-of-treatment IDUs and 35 methadone patients in New York City	Seroprevalence survey	87% of the out-of-treatment IDUs tested positive for HIV while 9% of those in methadone treatment tested positive.
Novick et al.	1985	IDUs from New York City with stored blood specimens	Retrospective seroprevalence	47% of the out-of-treatment subjects were found to be positive compared with 17% of the IDUs with five or more years of treatment.
Brown et al.	1988	360 methadone patients from Brooklyn, NY	Seroprevalence survey	Subjects with less than one year of methadone treatment were 1.5 times more likely to test positive.
Novick et al.	1990	58 New York City methadone patients with an average length of treatment of 17 years	Seroprevalence survey	None of the long-term methadone patients were found to be infected with HIV; at the time of the study, HIV prevalence among IDUs in New York City was estimated at 50%.
Blix and Gronbladh	1991	67 long-term methadone patients from clinic in Uppsala, Sweden	Seroprevalence survey	3% of the IDUs in long-term treatment were found to be infected with HIV; rates of HIV infection among IDUs in the community at the time of the study were estimated at 38%.
Williams et al.	1992	98 past or current methadone patients from clinic in New Haven, CT	Prospective seroincidence	2% of the subjects with continuous treatment seroconverted while 19% of those with interrupted treatment became infected; given small sample size, differences in incidence rates were not significant.
Metzger et al.	1993	152 IDUs in methadone treatment and 103 out-of-treatment IDUs from Philadelphia, PA	Prospective seroincidence	Significant association between treatment participation and HIV incidence; among subjects with stable treatment, 3.5% became infected, while 22% of those who remained out-of-treatment became infected.
Moss et al.	1994	681 methadone patients from San Francisco who had been tested at least twice	Observational seroincidence	An overall incidence rate of 1.9% per year was found; length of time in treatment was significantly associated with HIV infection (subjects with less than one year of treatment were three times more likely to become infected).
Serpelloni et al.	1994	40 Italian IDUs who had become infected during longitudinal study and 40 matched controls	Case control	Duration of methadone treatment and methadone dosage were significantly associated with protection from HIV infection.
Friedman et al.	1995	6882 IDUs with two or more HIV tests (subjects were recruited in 15 US cities while out of treatment)	Observational seroincidence	The only significant protective factor identified was participation in drug treatment.

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