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Human Immunodeficiency Virus Seroconversion Among Intravenous Drug Users In- and Out-of-Treatment: An 18-Month Prospective Follow-Up

David S. Metzger, George E. Woody, A. Thomas McLellan, Charles P. O'Brien, Patrick Druley, Helen Navaline, Dominick DePhilippis, *Paul Stolley, and †Elias Abrutyn

*University of Pennsylvania/VA Center for Studies of Addiction; †Philadelphia VA Medical Center and Medical College of Pennsylvania, Philadelphia, Pennsylvania; and *University of Maryland, Baltimore, Maryland, U.S.A.*

Summary: Our objective was to determine the prevalence and incidence of human immunodeficiency virus (HIV) infection and related risk behaviors among opiate-abusing intravenous drug users (IVDUs) either in or out of methadone treatment. The subjects, 152 in-treatment and 103 out-of-treatment intravenous opiate users, were followed prospectively for 18 months. Behavioral and serologic assessments were made at 6-month intervals, with complete information available on 89% of the sample. Subjects were recruited from a single methadone maintenance program and the surrounding neighborhood in north-central Philadelphia. At baseline, the HIV seroprevalence rate for the total sample was 12%: 10% for the methadone-maintained group and 16% for the out-of-treatment group. Out-of-treatment subjects were injecting drugs, sharing needles, visiting shooting galleries, and practicing unsafe sex at significantly higher rates than in-treatment subjects. Follow-up of HIV-negative subjects over the next 18 months showed conversion rates of 3.5% for those who remained in methadone maintenance versus 22% for those who remained out of treatment. The sixfold difference in rate of seroconversion between the two groups suggests that although rapid transmission of HIV still occurs, opiate-abusing IVDUs who enter methadone treatment are significantly less likely to become infected. In contrast, those opiate addicts who do not enter treatment are at significantly higher risk of contracting and spreading the disease. Implications for developing additional risk interventions for out-of-treatment IVDUs are discussed. **Key Words:** Human immunodeficiency virus—Prevalence—Incidence—Intravenous drug users—Methadone treatment—Risk interventions.

Stopping the spread of human immunodeficiency virus (HIV) among intravenous drug users (IVDUs) has become a national public health objective (1–3). Since the test for antibodies to HIV became available in 1985, studies conducted among IVDUs in the United States have found seroprevalence rates ranging from 0 to 61%. In examining factors associated with this marked variability in seroprevalence, past studies have identified both personal and situational characteristics, including city of drug use, drug of abuse, recency of injection initiation, access to new needles, and demographic characteristics (4–9).

While information from seroprevalence studies

Address correspondence and reprint requests to Dr. Metzger at University of Pennsylvania/VA Medical Center, Center for Studies of Addiction, 3900 Chestnut Street, Philadelphia, PA 19104, U.S.A.

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has been very useful in characterizing areas and populations at greatest risk of the disease, such studies cannot provide information on those factors within the high-risk regions and populations that are most associated with HIV *seroconversion*. Comparatively few studies have focused on factors associated with variability in seroconversion among IVDUs. This type of information could be particularly important to the planning and evaluation of educational, treatment, and other types of prevention interventions by permitting a more focused approach on those at particularly high risk within the IVDU group.

This report presents the results of a prospective, longitudinal study examining rates of both seroprevalence and seroconversion among IVDUs from Philadelphia over an 18-month period. In this effort we have built upon earlier studies of seroprevalence by focusing our efforts on IVDUs from within a single, high-prevalence community of the city. Because we thought that participation in methadone treatment could be an important marker of risky behavior (10–14) and HIV spread, we examined HIV prevalence and conversion rates separately among out-of-treatment (OT) and in-treatment (IT) cohorts of IVDUs from this community.

METHODS

In-Treatment Subject Recruitment

IT subjects were recruited from the outpatient methadone program of the Girard Medical Center, the largest methadone program in Pennsylvania with an average census of 440. This program is located in north-central Philadelphia, a neighborhood with areas of severe poverty, inadequate housing, and high rates of drug use. All patients in the program were invited to take part in the initial phase of this study beginning in July of 1989. Three hundred seventy-nine patients (86% of the clinic census) completed a self-administered questionnaire, which asked about their recent participation in AIDS high-risk behaviors.

One hundred fifty-two of those patients who completed the questionnaire were randomly selected using the sampling routine of the Statistical Package for the Social Sciences (SPSS). Each was asked to participate in the longitudinal serologic study. Seventy-two patients who did not keep their appointments were each replaced with a randomly selected alternate, producing a 68% (152 of 224) participation rate. Although five individuals reported that they did not wish to take part in the study because of their concern about HIV infection, the majority of nonresponders simply did not answer our request for participation. Analyses of demographic characteristics, drug use patterns, treatment histories, and risk behaviors did not identify any differences ($p > 0.05$ by t test or χ^2) among those who agreed to participate (n = 152), those who were not selected (n = 155), and those who did not respond (n = 72).

Out-of-Treatment Subject Recruitment

One hundred three OT subjects were recruited through referrals from IT subjects and by community outreach in the neighborhood surrounding the Girard Medical Center. Since we wanted a sample comparable to the IT subjects with regard to drug use, selection for participation was made after the completion of a brief, semistructured screening interview conducted by the research staff. To be eligible for study participation, referrals had to be >18 years of age, have a drug history that included a period of regular (at least three times per week) intravenous opiate use, and could not have been in any drug abuse treatment during the preceding 10 months. Subjects meeting these inclusion criteria were enrolled in the study. Twenty-five subjects were excluded because they did not meet the study criteria (most of them had no history of opiate use), and only three eligible subjects decided not to continue after learning more about the project.

PROCEDURE

All subjects were assessed at 6-month intervals. At each assessment point, subjects in both the IT and OT groups provided informed consent and were given pretest HIV counseling. Counseling sessions were designed to ensure that subjects were aware of the potential emotional impact of knowing their HIV status, that there was a possibility that a negative result could be found even after viral exposure, and that there were resources available for the treatment of HIV infection should they wish to take advantage of them. As part of counseling, risk-reduction strategies were discussed with all subjects, including instruction on how to use bleach and the importance of condom use. Also, all OT subjects were informed of the available treatment options and were encouraged to enroll.

Following pretest counseling, blood was collected and tested for antibodies to HIV using an ELISA technique with Western blot confirmation. Criteria for a positive Western blot required evidence of the presence of three viral components: p24, p31, and either gp41 or gp160. All specimens were tested by the Red Cross and were confirmed independently at a second laboratory; no discordant results were found.

Additionally, all subjects were assessed to determine their patterns of illicit drug use, participation in drug treatment, needle use, and sexual behaviors. The instruments used were the Addiction Severity Index (15), a 45-min structured interview that provides assessments of problem severity in seven functional areas commonly impaired among drug abusers; a modified version of the AIDS Initial Assessment (AIA) (16), a 30-min interview assessing participation in behaviors related to HIV transmis-

sion; and the Risk for AIDS Behaviors (RAB) (17), a self-administered questionnaire that also assesses needle-sharing and unprotected sexual activity. The staff conducting these interviews were knowledgeable about both substance abuse and HIV infection and were sensitive to the needs and concerns of IVDUs. Each subject was paid $20 for the assessment session, which typically lasted ~2 h.

Chi-square and *t* tests were used to compare the demographic and behavioral characteristics of the two samples at baseline. Differences in incidence rates between treatment groups were tested for significance using relative odds ratios. Probabilities of ≤0.05 were considered significant.

RESULTS

Demographic Comparisons

Table 1 presents comparisons of selected sociodemographic characteristics between the two cohorts at the beginning of the study. Comparisons found the OT sample to be younger (mean age of 38 versus 40, $p < 0.05$), with more blacks (78% versus 59%, $p < 0.05$) and more men (85% versus 69%, $p < 0.01$), than the IT sample. The groups did not differ by marital status or educational level. More IT subjects were working (25% versus 10%, $p < 0.01$), and while income was significantly lower among the IT subjects, fewer reported receiving money from illegal activity (15% versus 34%, $p < 0.01$).

TABLE 1. *Sample characteristics*

Characteristics	In treatment (n = 152)	Out of treatment (n = 103)	Significance
Age (yrs)	40 ± 8	38 ± 8	$t = 2.31$, $p < 0.05$
Gender (% male)	69%	85%	$\chi^2 = 7.81$, $p < 0.01$
Marital status			NS
Single/never married	43%	54%	
Married	23%	17%	
Separated/ divorced	28%	25%	
Widowed	6%	4%	
Race			$\chi^2 = 10.53$, $p < 0.05$
Black	59%	78%	
White	31%	17%	
Hispanic	9%	5%	
Other	1%	1%	
Highest grade completed	11	11	NS
Monthly income (median)	$196	$300	$\chi^2 = 8.01$, $p < 0.01$
Any illicit income	15%	34%	$\chi^2 = 11.93$, $p < 0.01$
Employed (% full- or part-time)	25%	10%	$\chi^2 = 9.39$, $p < 0.01$

Drug Use Comparisons

Age of initiation of drug use did not differ between the two samples, with both groups having used marijuana by age 17, heroin by 20, and cocaine by 27. With regard to treatment participation, the IT subjects had entered treatment more times than the OT sample (5.6 versus 3.5, $p < 0.01$). The average daily methadone dose among the 120 IT subjects reporting this variable was 44 mg (median = 45; mode = 50).

Although continued illicit drug use was reported by a substantial proportion of the IT sample (Table 2), the prevalence of drug use at the initial interview was consistently less than the OT sample. Overall rates of injection were significantly lower among IT subjects, and, for those who reported injecting, weekly heroin use was less than half as prevalent (33% versus 69%, $p < 0.01$), and cocaine injection was one-third as prevalent (22% versus 61%, $p < 0.01$) as in the OT sample.

The OT sample also reported engaging in more high-risk practices related to drug use (Table 2). Of those who reported injecting, a higher proportion of the OT sample had visited shooting galleries (55% versus 33%, $p < 0.01$) and crack houses (28% ver-

TABLE 2. *AIDS high-risk behaviors at baseline by treatment status*

Behaviors	In treatment (n = 152)	Out of treatment (n = 103)
Injection during previous 6 months[a]		
No injections	18% (27)	6% (6)
Injections but no sharing	48% (73)	24% (25)
Sharing 1–2 times	13% (20)	10% (10)
Sharing ≥3 times	21% (32)	60% (62)
Behaviors of those injecting during previous 6 months[b]		
Weekly injections during previous months		
Heroin	33% (40)	69% (61)[a]
Cocaine	22% (27)	61% (54)[a]
Combined ("speedball")	32% (39)	45% (40)[c]
Been to "shooting gallery"	33% (41)	55% (48)[a]
Been to "crack house"	11% (13)	28% (25)[a]
Report difficulty getting new needles	14% (17)	25% (22)[c]

[a] $p < 0.01$ by chi-square.
[b] Of those reporting injecting, two in-treatment subjects and nine out-of-treatment subjects had missing values for weekly injections, visiting "crack house," visiting "shooting gallery," or needle acquisition and were omitted from these analyses. For those in treatment n = 123; for those not in treatment n = 88.
[c] $p < 0.05$ by chi-square.

sus 11%, $p < 0.01$). More subjects in the OT group reported difficulty acquiring new needles (25% versus 14%, $p < 0.05$). Finally, the OT sample was engaging in needle-sharing at higher rates ($p < 0.01$) than the IT group. In fact, 70% of the OT group reported sharing needles at least once during the previous 6 months, as compared with 34% of IT subjects.

Few sexually active subjects from either group were using condoms on a regular basis (12% of the OTs and 15% of the ITs). However, the OT group reported a higher average number of partners (4.6 versus 2.3, $p < 0.01$) during the previous 6 months and more frequently engaged in commercial transactions for sex (46% versus 28%, $p < 0.01$).

Follow-up Rates Over 18 Months

Serostatus was determined for 91% (138 of 152) of the IT subjects at each follow-up point during the first 18 months of study. One subject who was HIV positive at baseline died between months 12 and 18 from HIV-related illness. Four of the 14 subjects whose serostatus was unknown also died. The cause of death in one case was drug overdose; two died from alcohol-related illness; and one died from "massive infection." Of the remaining 10 subjects, we were unable to locate one, another did not wish to continue, six were interviewed while incarcerated but were unable to have blood drawn, and two had inaccessible veins.

Among the OT group, serostatus was determined at each follow-up point for 85% (88 of 103) of the subjects, including one HIV-positive subject who died after the 12-month follow-up from an AIDS-related illness. Nine of the 15 OT subjects whose serostatus was unknown at the 18-month follow-up could not be located. Of the remaining six subjects, three were incarcerated, and three were residing out of state. Although these six subjects completed interviews, we were unable to obtain blood specimens.

To examine the potential impact of attrition, baseline data provided by subjects whose serological status was unknown at the 18-month follow-up were compared with retained subjects who were HIV negative at baseline. A higher proportion of the subjects (n = 29) who were lost to follow-up were sharing needles (65% versus 45%, p = NS), were engaging in unsafe sex (48% versus 31%, $p < 0.05$), and were likely to have purchased a needle in a shooting gallery (57% versus 33%, $p < 0.05$). Thus, those who were lost to follow-up were more often engaging in behaviors known to increase the risk of HIV infection than those who were retained. These differences did not differ between the two cohorts.

HIV Prevalence

Prevalence rates were calculated using only those subjects with complete serologic data. Figure 1 presents the infection rates for the subjects (n = 226) whose serostatus was known at all four assessment points. For these subjects, infection rates rose over an 18-month period from 11% (15 of 138) to 15% (21 of 138) among the IT sample and from 18% (16 of 88) to 33% (29 of 88) among the OT sample. These prevalence rates differed significantly at both 12 months ($p < 0.01$) and 18 months ($p < 0.01$).

HIV Incidence

These increasing prevalence rates reflect the seroconversion of 6 (4.4%) IT subjects and 13 (14.8%) OT subjects, producing an overall incidence rate of three conversions per 100 person years of exposure for the IT cohort and 10.7 conversions per 100 person years of exposure for the OT cohort. As seen in Table 3, incidence within each cohort varied by follow-up interval. Among the IT cohort, respective 6-month incidence rates were 4.5 conversions per 100 person years of exposure during the first interval. This number dropped to 3.3 in the second interval and to 1.7 during the third interval. Among the OT cohort, dramatically higher incidence rates

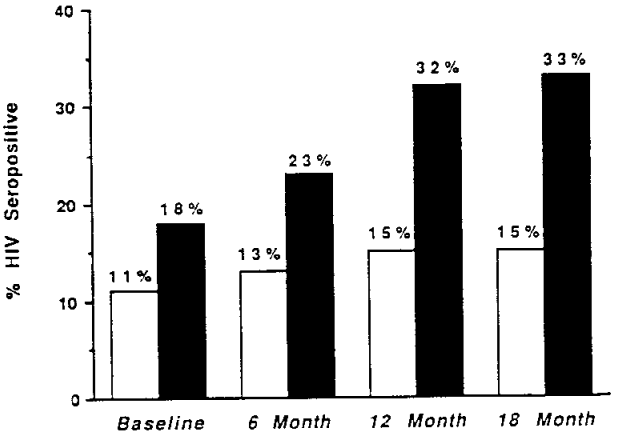

FIG. 1. HIV infection rates by baseline treatment status. White bars, in treatment (n = 138); black bars, not in treatment (n = 88).

TABLE 3. *HIV prevalence and incidence by initial treatment status*

	In treatment			Out of treatment		
	No. pos/ no. tested	% Pos	Incidence per 100 person yrs	No. pos/ no. tested	% Pos	Incidence per 100 person yrs
Initial assessment	15/152	10%	—	16/103	16%	—
6 Months	18/146	12%	4.6	20/88	23%	11.1
12 Months	20/138	15%	3.3	28/87	32%	23.9
18 Months	21/138	15%	1.7	29/88	33%	3.3

Pos, positive.

were found. Seroconversion occurred at a rate of 11.1 per 100 person years of exposure during the initial interval. This rate rose to 23.9 during the second interval and dropped to 3.3 during the final interval.

Seroconversion and Treatment Participation

During the course of the study, 15 OT subjects entered methadone treatment, and 42 IT subjects left treatment. To further examine the relationship between treatment participation and seroconversion, all of the initially seronegative subjects with complete serologic data (n = 185) were grouped according to their participation in methadone treatment over the 18-month study period. Forty-six percent (n = 85) were in methadone treatment at all points, 24% (n = 45) were in treatment at one, two, or three points (intermittent treatment), and 30% (n = 55) were not in methadone treatment at any point.

As seen in Fig. 2, 3.5% (three of 85) of those in treatment at all points became HIV positive by 18 months; 4.4% (two of 45) of the intermittent treatment sample seroconverted, and 22% (12 of 55) of the untreated sample seroconverted. Compared with the group who was in methadone treatment at all points, the odds of seroconversion were 7.63 among the untreated subjects (CI = 1.99–29.27; $p < 0.01$) and 1.08 (NS) for the intermittent treatment group. Thus, the subjects who remained out of methadone treatment were 7.63 times more likely to become HIV positive during the 18-month study period than those who remained in treatment. Furthermore, the untreated group was six times (CI = 1.23–29.34; $p < 0.05$) more likely to seroconvert than the intermittent treatment group. Both of the seroconverters in the intermittent treatment group began the study in treatment, and each had been out of methadone treatment during the 6 months before their seroconversion.

Multiple logistic regression was used to determine the relative odds of seroconversion while controlling for race, gender, age, and needle-sharing. Although the odds of seroconverting relative to the treated group were somewhat lower (OR = 5.39; CI = 1.64–17.77; $p < 0.01$) with these variables in the equation, treatment status remained as the only significant factor.

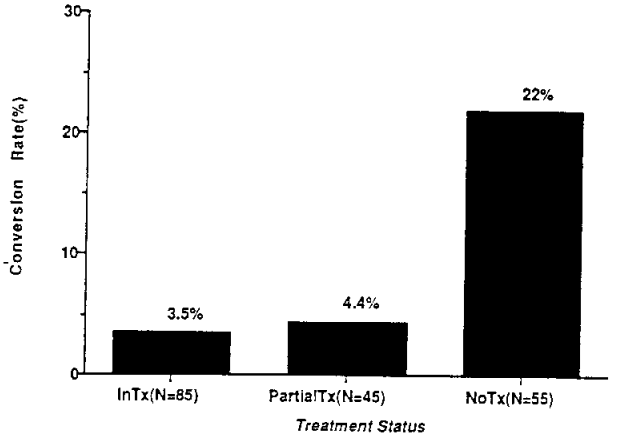

FIG. 2. Eighteen month HIV conversion by treatment retention.

COMMENT

These data provide an examination of seroconversion and high-risk behaviors among two cohorts of IVDUs. The prevalence of HIV infection in the overall group of 255 opiate addicts was 12% at the beginning of the study. Eighteen months later, this figure had increased to 22%. These aggregate data therefore provide confirmation of other studies showing that as a group, IVDUs continue to be at significant risk for becoming infected with HIV. The incidence rates reported here are higher than any previous U.S. study and thus require careful interpretation (1,18,19). We are not suggesting that all IVDUs in Philadelphia continue to seroconvert

at a rate of 15% every 1.5 years. In fact, even within this sample, by the final 6-month interval, seroconversion rates had dropped to 2.2%. It is quite likely that these data merely reflect the pace with which the virus can spread among IVDUs, moving rapidly within active needle-sharing groups in concentrated geographic areas. The prospective nature of this study allowed us to capture this phenomenon during a relatively short period. Undoubtedly, similar rapid "bursts" of infection have occurred in other high prevalence areas, such as New York City, where retrospective data suggest that seroprevalence rates rose from <20% to 50% in just 3 years (8).

The finding that 3.5% of those who continued to participate in methadone treatment throughout the 18 months of observation seroconverted, while 22% of those who remained out of methadone treatment seroconverted is striking. Although these differences suggest that methadone treatment reduces the incidence of seroconversion, several aspects of this study prevent such a definite conclusion. These aspects include the self-selected nature of treatment participation, the relatively small sample size, the nonprobability techniques used in the recruitment of OT subjects, and the focus on a particular neighborhood within a single city. These factors do limit our ability to generalize the findings. Yet it is important to note that the IT subjects were randomly selected and appear to be representative of the larger clinic population from which they were drawn. The OT subjects were referred by IT subjects and were typically members of their social networks. In addition, OT subjects were similar to IT subjects with regard to their abuse of opiates, education levels, and marital status. Given the high rate of subject retention, it is unlikely that our findings are a reflection of the effects of attrition. In fact, when compared with those who were retained, those subsequently lost to follow-up (12%) reported higher rates of risky behavior, suggesting that incidence rates might have been even higher had we been able to retain all subjects.

Although it is possible that long-term methadone treatment helps prevent HIV infection by normalizing immune function in IVDUs (20), the difference in these incidence rates is more likely due to differing levels of risk behaviors (Table 2). Yet because of the limitations cited above, we cannot conclude that the lower rates of risk behaviors are the direct effects of the methadone program. Furthermore, because of the known efficacy of methadone treatment, it was not possible, and it may never be possible, to randomly assign IVDUs who apply for treatment to conditions of methadone versus no treatment. It is also important to note that past studies have not consistently found an association between methadone participation and lower levels of seropositivity (21,22). Thus, the lower rates of HIV risk behaviors found among the IT subjects may be independent of their treatment participation, a conclusion that agrees with the comparably lower incidence rate found among those who were treated only part of the time.

While treatment status at the time of recruitment may simply be a marker for motivation and lower rates of needle-sharing, there is evidence to support the conclusion that methadone treatment is causally related to the lower levels of risk behaviors and seroincidence observed here. First, numerous studies have now documented the effectiveness of methadone treatment in helping patients reduce their use of opioids and other illicit substances as well as needle-sharing (10–13). The data reported here are in agreement with this body of research. Also, given the high rate of relapse to drug use known to occur after methadone treatment, it is unlikely that reductions in risk behaviors could be maintained without the ongoing support of the treatment program (23). In this regard it is important to note that the two subjects treated intermittently who seroconverted began the study while in treatment and became infected after leaving treatment, suggesting that discontinuation of treatment may be a marker for high-risk behaviors.

As reported, high-risk behaviors did not cease among IT subjects. In fact, participation in risk behaviors remained unacceptably high among those in treatment. However, their rates of seroconversion were two to three times lower than those of the OT group. We have examined characteristics associated with continued needle-sharing among IVDUs in methadone treatment and found that the subgroup who continued to share were characterized by higher levels of psychiatric symptoms and less time in treatment (24).

Implications for Out-of-Treatment IVDUs

Regardless of whether the comparatively lower rates of HIV seroconversion among the IT cohort were due to preexisting subject differences, the direct effects of treatment, or to a combination of these factors, the results of this prospective study

offer some cause for optimism about IVDUs who are in methadone maintenance. In contrast, the high-risk behavior and elevated incidence of HIV infection observed among the OT subjects suggest these IVDUs are at substantial risk for both acquiring and spreading HIV. In fact, these data may actually underestimate incidence in the larger community, since our contact with these OT subjects included repeated HIV testing and education, potential interventions that are often not readily available to IVDUs who are not in treatment.

It is possible that intensified outreach efforts could draw more IVDUs into methadone maintenance or other forms of drug treatment and that participation in treatment would produce positive changes. However, we believe that novel and more creative approaches to treatment will be required to achieve this goal. Eighty percent of the OT subjects had been in methadone maintenance an average of three times and were quite familiar with other treatment options. Moreover, these subjects were encouraged by our staff to enter treatment, but almost all rejected these offers despite the fact that treatment was readily available, with no waiting lists and at no cost. Clearly, traditional approaches to substance abuse treatment were not very attractive to these OT subjects.

Our success in subject recruitment and retention, however, does suggest that these individuals were interested in their HIV serostatus and were willing (with payment incentives) to participate in behavioral and serologic assessments and in brief counseling sessions over the 18-month period of monitoring. It is important to note that our ability to engage out-of-treatment IVDUs in activities of this type is not unique (25–28). Although retention rates in this study are unusually high, groups have been able to locate and enroll out-of-treatment IVDUs in programs of risk-reduction education, serologic testing, and counseling. Clearly, under some circumstances, untreated opiate-abusing IVDUs are reachable and can be engaged in at least minimal levels of intervention. Thus, we feel that a major finding of this study is the ongoing participation of these "treatment resistant" IVDUs who appear to be at greatest risk of HIV infection and transmission. Perhaps these tentative steps toward treatment could be expanded by new pharmacotherapies, such as buprenorphine, that are effective and more attractive to a broader base of the IVDU population (29). It is also clear that IVDUs will be attracted to and retained by those interventions that address their extensive unmet basic needs (e.g., housing, food, and financial support), either directly or through the establishment of closer links between substance abuse treatment and other important social services.

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