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Methadone Treatment Protects against HIV Infection: Two Decades of Experience in the Bronx, New York City

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SYNOPSIS

Objectives. We undertook a study of the role of methadone maintenance in protecting injecting drug users (IDUs) from human immunodeficiency virus (HIV) infection from the earliest days of the HIV epidemic in New York City to the present. The historical context of the epidemic in the Bronx is discussed.

Methods. For close to two decades, we have been tracking changes in injecting drug use and HIV infection levels in a Bronx cohort study of IDUs. An initial sample of 622 IDUs was recruited from a methadone treatment program in 1985, with historical data going back to 1978. Behavioral interviews and HIV testing were performed and methadone treatment program records (urine toxicology and methadone dose history) were reviewed. We examined both prevalent and incident HIV infections. The sample included African Americans (24.3%), Latinos (50.3%), and white non-Latinos (24.4%). The average methadone dose was 64 milligrams (mg) per day with an average time in treatment of five and a half years.

Results. We found a very low rate of incident infection of 1.7 per 100 person-years observation since 1986. Because of this low rate of infection, we were unable to determine the association between methadone treatment factors and HIV seroincidence. We found that our prevalence data on the 622 IDUs enrolled from 1985 to 1988 yielded strong findings on the role of

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methadone maintenance in a period when most infections occurred in this population. HIV seroprevalence was 42.9%.

Logistic regression analysis revealed associations of methadone dose ≥80 mg (adjusted odds ratio = 3.07/yr, 95% confidence interval (CI): 1.23–7.68) and last year entered methadone treatment (adjusted odds ratio = 1.22/yr, 95% CI: 1.06–1.41) to HIV infection, independent of year of last cocaine injection, needle sharing in shooting galleries, number of IDU sex partners, low income, and African American or Latino ethnicity.

Conclusions. Properly dosed, long-term methadone treatment was found to be a central protective factor in preventing HIV infection from the earliest days of the epidemic in New York City. It is crucial to have high quality drug treatment programs in place before an epidemic draws our attention to the inadequacies through excess and unnecessary morbidity and mortality.

Methadone maintenance as a treatment for opiate addiction has been under intensely negative scrutiny since its first use in the United States in the late 1960s.[1] By the time injecting drug use was recognized as a major factor in human immunodeficiency virus (HIV) infection transmission, methadone treatment had become a modality of last resort, unwanted by the public as well as injecting drug users (IDUs) in need of treatment.[2] Despite almost two decades of experience with HIV infection among patients in methadone clinics in this country and strong early consensus on its value in preventing infection,[3,4] direct data on specific HIV protective factors have not been well studied, particularly data on methadone dose.

Methadone maintenance is currently considered part of the multilevel approach to reduce the consequences of drug use such as HIV, hepatitis, homelessness, and other conditions among IDUs worldwide.[2] As an opioid agonist, methadone obviates the need for other opiate-based drugs among individuals with demonstrated opiate tolerance and withdrawal syndrome.[5,6] The literature on methadone maintenance in reducing heroin use and injection indicates a number of factors likely to underlie reduced drug and needle use which may protect individuals from acquiring HIV: methadone dose,[7–10] duration of methadone treatment,[10–14] treatment compliance,[9,12] and counseling.[15]

HIV infection among IDUs varies widely in the United States.[16] Despite large numbers of seroprevalence studies reported among IDUs, few have focused on methadone treatment factors. To date, studies that included methadone factors have shown only simple associations between methadone treatment duration and HIV infection.[17–22] Methadone dose, a central treatment factor, has been shown to be related to HIV seroconversion in only one study,[21] although dosages were relatively low in this small case-control series (n = 40 cases). The most striking findings have been comparisons of in-treatment and out-of-treatment infection rates: 3.5% vs. 22% in 18 months of follow-up.[17] Williams and colleagues[19] found a similar difference.

For the most part, examination of methadone treatment factors associated with HIV seroconversion in the studies cited above have been limited by low numbers of newly infected patients in treatment and short periods of follow-up. Our own cohort study has a relatively long observation period on seronegatives with two or more follow-up visits (n = 607), but has a low seroincidence rate of 1.7 per 100 person-years of observation.[23] Other seroincidence rates among methadone in-treatment patients are similar.[17–20]

In the early period of the HIV epidemic, we as well as others concentrated on risky drug injecting and sexual behaviors but neglected specific methadone treatment factors. Later, methadone treatment itself emerged as an important prevention strategy, but the rate of new infections (seroincidence) was low due to a number of factors, including infection saturation of the high risk population.[24] In this way, an opportunity to study methadone treatment factors in relation to HIV infection was nearly lost. In an effort to remediate this problem, we have undertaken a new analysis of our early epidemic seroprevalence data. This analysis provides a means to examine methadone dose, treatment duration, counseling, and known drug and sex risk behaviors in the well-studied population of Bronx IDUs.

As background to this study, it is important to know that there have been large-scale temporal changes in types of drugs injected among IDUs in the Bronx as elsewhere. This is important in studies of methadone maintenance, as methadone is a treatment specific to opiates but not stimulants such as cocaine and amphetamines. A study of early epidemic injecting trends in our cohort demonstrated a rapid rise in cocaine injecting starting in 1978 and stabilizing in 1983.[25] From 1985 to 1993 we have since seen a decline in cocaine injecting, but relatively stable injecting of heroin.[23]

To address these gaps in the literature, we undertook an examination of drug treatment factors (methadone dose, duration, compliance as per urine toxicology results, and counseling) in relation to HIV infection status in our early seroprevalence sample obtained in 1985. We added these variables to our previously published model of risk factors for HIV infection among IDUs in the Bronx, New York, which included drug injecting and needle sharing; sexual risk behavior; and social, demographic, and economic factors.[26] Since most participants were enrolled in the study just as HIV antibody tests first became available, these injecting histories likely represent a "natural" test of the preventive effects of methadone treatment without the force of widespread HIV counseling, testing, and education in this population.

METHODS

The study sample and methods of HIV testing, risk factor history-taking, and statistical methods of analysis have been previously described by Schoenbaum and colleagues.[26] We briefly summarize our sample and methodology, emphasizing drug treatment variables used in this analysis.

Beginning in 1985, patients in the Montefiore Medical Center Methadone Treatment Program were enrolled in a study of HIV risk factors. The majority of patients were enrolled by mid-1986 but enrollment continued until 700 patients had been interviewed (completed in 1988) regarding their HIV risk behavior (drug-injecting and sexual practices). Serum samples were obtained from 96% of these patients and were tested for the HIV antibody. Variables previously associated with HIV infection included year of last drug injection (heroin, cocaine, or speedball), percentage of injections in shooting galleries, number of IDU sex partners, race or ethnicity, and income. HIV antibody was determined using Genetic Systems' enzyme-linked immunoabsorbent assay (ELISA). Specimens repeatedly reactive on ELISA were tested by Western blotting and were considered positive when antibodies to p24 and gp41 were detected.

A new set of variables was derived from methadone clinic records. These included methadone treatment duration (cumulative time in treatment), year of first treatment entry and average methadone maintenance dose, presence of methadone in urine (compliance measure), and treatment counselor assignment (counseling measure). Methadone maintenance dose was calculated as a time-weighted average of the patient's dosage history as of his or her interview date. Periods of rapid dosage escalation on entry into treatment were excluded from this calculation. For the majority of patients, once stabilized, dosage changes were minimal (median change: 10 mg).

Urine toxicology test results were available in clinic records for all patients in this sample. The primary metabolite of heroin, morphine, was tested by enzyme-multiplied immunoassay (EMIT) confirmed by thin layer gas chromatography. A set of five urine tests within three months of interview were used to examine the validity of self-report drug abstinence in that period. In addition, presence of methadone in the urine was used as an indicator of methadone compliance.

The sample for the current analysis included 622 participants, after excluding two with indeterminate HIV antibody test results and 49 who never injected drugs. Logistic regression was used to model risk factors for HIV infection. Since risk factor models had been developed previously for the first 500 individuals enrolled in the prevalence study (452 IDUs with sufficient data), models were first constructed using these previous findings. We added methadone treatment variables (described earlier) to the original model as well as an interaction term for treatment duration and dose. A second modification of the original model was made by separating date of last

heroin injection (including speedball injection) from date of last cocaine injection. We hypothesized that any protective effect of methadone dose is mediated through reduction in injecting heroin use but not cocaine use. This assumption is based on other studies in this population, in which we found cessation of heroin use but not cocaine use highly associated with methadone dose.[9] Model parameters were estimated using maximum likelihood methods; variables with a probability of association with HIV status of <0.10 were retained in final models.

RESULTS

This sample of 622 methadone-maintained patients was of generally low socioeconomic status: 69.8% with income under $10,000 per year, 53.2% without a high school diploma, 62.5% currently unemployed, and 18.6% homeless in the year prior to interview. The average maintenance methadone dose was 64 mg/day, and the average time in methadone treatment was five and a half years. There were 151 patients (24.3%) in the sample who described themselves as African American, 313 (50.3%) as Latino (mainly of Puerto Rican descent), 152 (24.4%) as white, and six (1%) as not belonging to any of these three groups. Women accounted for 49% of patients.

A comparison was made between the 622 patients in this sample and the entire clinic population in treatment during the enrollment period (n = 1560). In comparison with the rest of the clinic patients, the study sample had a statistically significant (P < 0.05) higher average dose of methadone (64 mg/day vs. 59 mg/day) and a greater proportion enrolling in treatment before 1982 (36% vs. 31%). No other variables, including age, race or ethnicity, gender, education, income, and pattern of drug use, differed between the two groups.

Overall HIV seroprevalence was 42.9% (267 out of 622). The relationships between the treatment variables under examination in this analysis and HIV infection status are displayed in Table 1. Patients on methadone dosages of 80 mg/day or higher had the lowest infection levels. The odds of HIV infection among patients on dosages of less than 80 mg/day compared to those on higher dosages were 1.95 times greater. Analysis of dose data in 10 mg/day increments in association with HIV infection status showed a threshold-type dose effect—an overall similar level of infection in all dosage groups less than 80 mg/day—and the same overall lower level of HIV in patients maintained on 80 mg/day or more of methadone.

The association between methadone dose and HIV differed by treatment entry year. There was a 52.9% seroprevalence level among patients entering treatment in 1985 or later, compared with 44% for those entering in 1980 through 1984 and 34.1% among those entering before or during 1979.

Variables previously reported as risk factors for presence of HIV antibody did not differ from our past findings. Associations between HIV status and sharing needles in shooting galleries, sex with an IDU, year of last injection (cocaine), income, and race or ethnic background are summarized in Table 2. The association between methadone dose and HIV differed by treatment entry year. Patients in treatment before 1983 with dosages under 80 mg/day were 1.54 times more likely to become infected with HIV compared with those on higher dosages in treatment during the same period (40% vs. 30%). For more recent entrants (during or after 1983),

Table 1. Methadone treatment variables associated with HIV antibody status

Variable	HIV status		Odds ratio	95% CI
	Percent	Number		
Methadone dose (mg/day)				
<60	45.0	(154/338)	1.97	1.21–3.22
60–79	44.7	(85/190)	1.91	1.13–3.23
>80	28.0	(28/94)	1.00	Reference
Year last entered methadone				
1985 or later	52.9	(90/170)	2.17	1.44–3.28
1980–1984	44.0	(102/232)	1.52	1.04–2.22
1979 or earlier	34.1	(75/220)	1.00	Reference
Cumulative years in methadone				
<1	48.3	(42/87)	1.50	0.94–2.40
1–5	50.1	(81/160)	1.65	1.13–2.39
>5	38.4	(142/370)	1.00	Reference

patients on less than 80 mg/day maintenance dose were 2.29 times more likely to become infected than those on higher dosages (53% vs. 33%). There was no association of counselor assignment or presence of methadone in urine to HIV infection.

Logistic regression analysis revealed that methadone dosages of less than 80 mg/day were associated (adjusted odds ratio = 3.1, 95% CI: 1.2–7.7) with HIV infection after adjustment for all other variables under examination

(Table 3). There also was an independent effect for most recent year of entry into treatment. Year of treatment entry also was selected for modeling rather than the number of months or years in treatment, as the former measures both time since start of treatment (duration) and the point during the HIV epidemic in New York City (epidemic year) at which an individual enters treatment. Consistent with stratified analysis described earlier, there was a statistically significant interaction between year

Table 2. Variables other than treatment associated with HIV antibody status

Variable	HIV status		Odds ratio	95% CI
	Percent	Number		
Needle sharing in shooting galleries				
Yes	60.0	(117/195)	2.77	1.95–3.93
No	35.1	(150/427)	1.00	Reference
Year of last cocaine injection				
1985 or later	54.0	(182/337)	6.97	3.16–8.78
1980–1984	39.7	(69/174)	3.90	2.12–7.19
1979 or earlier	14.4	(16/111)	1.00	Reference
Sex partners who inject drugs				
2 or more	52.2	(85/163)	1.66	1.16–2.38
<2	39.7	(182/459)	1.00	Reference
Race/ethnic background				
African American or Latino	49.8	(231/464)	3.58	2.33–5.48
White and non-Latino	21.7	(33/152)	1.00	Reference
Income (per year)				
<$10,000	47.2	(205/434)	1.44	1.02–2.05
$10,000 or more	38.3	(72/188)	1.00	Reference

Table 3. Logistic regression: independent associations with HIV antibody status

Variable	Adjusted odds ratio	95% CI	Wald χ^2
Methadone dose (mg/day)			
≥80 mg vs. <80	3.07	1.23–7.68	5.75
Year last entered methadone			
(per year)	1.22	1.06–1.41	7.78
Year of last cocaine injecting			
(per year)	1.18	1.12–1.25	33.28
African American or Latino			
vs. white	3.47	2.18–5.52	27.71
Needle sharing in galleries			
(any vs. none)	1.90	1.29–2.81	10.54
Income			
≥$10k vs. <$10k	1.69	1.06–2.53	6.51
IDU sex partners			
>1 vs. ≤1	1.47	0.97–2.22	3.38

NOTE: A statistically significant ($P = 0.05$) interaction term for "methadone dose" × "year last entered methadone" was included in this model.

of most recent entry and methadone dose in relation to presence or absence of HIV infection.

Other variables meeting model retention criteria were year of last cocaine injection, sharing needles in shooting galleries, having two or more drug user sex partners, low income (<$10,000), and self-identification as a member of a racial or ethnic minority group. There was no discernable effect for counseling during treatment. The only information available to us was counselor assignment, which was used as an indirect measure of the quality of counseling. There may be an effect of counseling, but we were not able to detect it with the data on hand. These findings were not altered by exclusion from analysis of individuals with discrepant urine and interview drug use data and of individuals with no methadone found in their urine.

DISCUSSION

The finding of central importance in this study was the strong association between methadone dosages of 80 mg/day or higher and low prevalence of HIV infection at the outset of the epidemic of HIV in the Bronx. This threshold-type dose effect is consistent with the upper limit of the National Institute on Drug Abuse (NIDA) recommendation of 60 to 80 mg/day as an effective dose range for stable, long-term reduction of opiate use.[4,10] Furthermore, our previous studies have shown a similar dose-effect threshold at 70 mg/day in association with a high degree of abstinence from heroin among methadone patients.[9] This dosage level is the lower limit of the 80 to 120 mg/day dosages administered in landmark methadone studies in the 1960s and early 1970s that observed "narcotic blockade" of other opiates at this level.[5,6] In theory, such high dosages of methadone provide mu-opioid receptor coverage sufficient to block other opiate effects, alleviate opiate craving, and prevent opiate abstinence syndrome from occurring. A careful review by Hargreaves[7] found most studies prior to 1983 showed reduction of heroin use with dosages above 50 mg/day, with strongest effects at 80 mg/day or higher. More recent examination of methadone dose effects on heroin use have shown dosages of 80 mg/day to be highly effective in a prospective study of Australian methadone patients.[8]

In this current study, we observed longer time in treatment to be associated with a lower probability of HIV infection. This association consists of two major components: cumulative time in treatment and year of treatment entry. Time in treatment has long been related to reduction in opiate use in reviews of the methadone literature[3,4,12] as well as our own more recent work.[25] Several other studies of HIV in methadone patients have shown treatment duration, especially uninterrupted treatment, to be associated with low HIV infection risk.[17–19,21] In our present analysis, overall treatment duration was less important than year of most recent entry into treatment as a protective factor in HIV infection. In our data, protection occurred for injecting heroin users who entered treatment early in the epidemic and who remained in treatment continuously. Apparently, gaps in treatment placed individuals at renewed and increasing risk of infection in a period of rising community infection levels.

As expected, cocaine injecting remained an independent risk factor for HIV infection, as methadone maintenance is not a specific treatment for cocaine use. Not only is cocaine injecting not reduced by methadone, it may actually interfere with the dose response of methadone on heroin use, as we have shown.[9] Cocaine may thus be associated with HIV both as an independent risk behavior and through pharmacologic interference in methadone's reduction of heroin injecting. Fortunately, there is no evidence of "substitution" of cocaine for heroin during methadone treatment.[27] Increases in cocaine injecting in our own data during the early epidemic years were clearly part of an overall temporal trend and not due to treatment effects.[25] Analyses of later trends showed a decline in cocaine injecting from the late 1980s through the 1990s among IDUs.[23,28,29] The earlier increase in cocaine injecting as part of a temporal trend exacerbated the conditions for exposure to HIV among IDUs in the Bronx and elsewhere in the United States.[27,30]

Cocaine may be a particularly risky injecting behavior for HIV given the typical high daily injecting rate compared with injected heroin[22,26] and the tendency to share needles in high risk settings such as shooting galleries.[30] The pharmacologic properties of cocaine itself may be related to these high risk patterns of behavior for several reasons. The 20-minute half-life of euphoria, primarily mediated by elevation of dopamine concentrations, is followed by a sharp drop in these concentrations resulting in dysphoria and intense drug craving.[31] The heaviest cocaine users tend to inject several times per day for three to four days at a time, a rate considered binge use. Moreover, cocaine often produces a mental state in which personal safety may be disregarded to a greater degree than observed with nonstimulant drugs.

To further clarify the associations among drug treatment variables, cocaine injecting, and HIV infection found in our data, we also examined needle sharing in shooting galleries, sexual risk behavior, and socioeconomic

variables. In New York City, shooting galleries were likely the locus of the initial epidemic increase among injecting drug users.[32] While needle sharing is the known means of infection acquisition, settings such as shooting galleries provided a high probability of sharing equipment with infected individuals.[33] In the early part of the epidemic in New York City, the period from which these data are drawn, this type of sharing predominated in the HIV infection risk profile.[26,34] As in our previous study, shooting galleries remained an important independent risk factor for HIV infection. The epidemic in New York City has seen a sharp drop in shooting galleries and in needle use and sharing, often replaced by intranasal and inhalation use of drugs.[35] These changes are welcome, but should be viewed as relatively fragile. Any change in conditions that currently supports reduced needle sharing, such as a decreased heroin purity that renders snorting ineffective, or the abolition of needle exchange programs, can result in a sudden upsurge in risky behavior and preventable new infections.[36]

Sexual risk behavior is a less efficient means of HIV transmission than needle sharing,[33] and our data show an independent but relatively small associated effect size for sexual risk behavior. In New York City, the greatest risk for infection in the heterosexual population continues to be contact with an IDU,[37] and IDUs play a central role in maintaining high background levels of infection in some communities such that sexual transmission can be sustained.[38] The independent association for race and ethnicity in our data is consistent with national trend data for that time period, showing the virus affecting impoverished communities of color to a greater degree than other subpopulations. The increased risk for African Americans and Latinos likely reflects higher background prevalence and increased likelihood of contact with an infected person during the study period.[38]

While our data indicated that lower income was independently associated with HIV infection, this variable gives little flavor of the events in the Bronx at the time. A worsening economy set the stage for the rapid destructive course of HIV. At the time of our initial study, the Bronx was in tremendous upheaval. There was a well-documented migration of Bronx residents due to breakdown of the infrastructure with widespread uncontrolled residential fires, resulting in the breakup of communities and social networks.[39,40] The well-documented cocaine epidemic came on the heels of this community breakdown, further destroying the fragile human ecology of the Bronx.[41] HIV entered the scene at the same time, with rapid infection transmission through needle-sharing networks that were

in great flux, with many individuals resorting to sharing needles with large numbers of strangers in shooting galleries.[42] A mathematical model-based examination of the probable dates of seroconversion in our population shows that most infections occurred by 1983,[43] with a relatively stable seroprevalence reached by 1985 as described for New York City as a whole.[32]

The role of counseling not found to be related to HIV infection in these data bears comment. A relatively recent study underscored the importance of counseling,[15] long an integral part of methadone maintenance as originally formulated by Dole and colleagues.[5] Counselors bear tremendous responsibility for integration of services, HIV risk reduction counseling, drug use education, and even for negotiating dosage changes on behalf of clients.[44] Unfortunately, some counselors harbor punitive and anti-maintenance attitudes.[45] In clinics in New York and Australia, we found that belief in short-term treatment and in reduction of dosage as a punishment for continued drug use was common despite clear program policies to the contrary. The attitudes of the treatment program staff must be examined, as staff can make the difference between an effective program and one that merely goes through the motions. Since punitive attitudes toward drug users and general distaste for methadone maintenance are found throughout the United States and other countries,[46] it is not surprising to find such attitudes among treatment staff. It is especially disturbing, however, to find such attitudes among staff members with the most frequent patient contact. Treatment programs need to establish effective screening, regular education, and psychological support of staff as they deal with the complicated and demanding work of addiction treatment.

Our two decades of experience with methadone maintenance among IDUs in the Bronx underscores the importance of prevention planning with a sense of history without giving in to superficial or fear-driven political forces. By the late 1970s in the United States, methadone had expanded rapidly and was largely effective in making heroin addiction a less visible problem, but it was viewed as immoral and permissive. At the time, it was politically correct to undermine programs with reduced dosages and time in treatment.[1,47] No one could have anticipated that methadone programs, unpopular as they were, would play a crucial role in protecting IDUs against a devastating and deadly emergent virus. Nor did anyone anticipate the effects of the cocaine epidemic, considered a relatively harmless drug in the 1970s.[48] While the vast majority of cocaine users are occasional and not addicted, more cases of extreme use occurred among those already addicted to

heroin. Since that time, decreases in cocaine injecting have shown up in our data as well as in national databases.[23,49] The downturn in cocaine use and injecting since that time is heartening but should not lead to deemphasis on multimodality treatment and risk reduction programs for IDUs. While there has been an overall temporal decline in injecting behavior with some switching to noninjecting drug use throughout the country,[50] there are local variations.[51] Even in those areas showing positive changes in risk behavior, there may be a return to injecting drug use when conditions supporting noninjecting drug use change. Intense socioeconomic disruption of neighborhoods, important to the rapid dissemination of HIV in the Bronx, also can happen in the future—and not just in the Bronx.

CONCLUSION

This study demonstrates strong protective associations against HIV infection for high dose methadone treatment and early entry into and continuous stay in methadone treatment, independent of cocaine injecting, shooting gallery injecting, and sex with other IDUs. Properly dosed methadone treatment remains a strong element in a comprehensive public health approach to HIV infection control. Our data on methadone treatment go back to the earliest days of the epidemic in the Bronx in 1978. It was a period of rapid change: breakdown of neighborhoods and social networks, rapid increase in cocaine injecting and shooting galleries, an all-time low in the popularity of methadone maintenance programs, and tremendous resistance to needle exchange and risk reduction in general.[36,46,47] There had even been a movement to lower methadone dosages from the optimal levels described in early studies of methadone.[1] Against this background, individuals who were lucky enough to get into methadone treatment, be placed on a sufficiently high dosage, and remain in treatment were largely protected from acquiring HIV. Early protection was essential in our studies as the virus rapidly moved through this population, saturating it early. Methadone maintenance continues to quietly hold the line against HIV infection, even when it is close to impossible to study in current, short-term epidemiologic studies.

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