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**A CONTROLLED TRIAL OF METHADONE TREATMENT
COMBINED WITH DIRECTLY OBSERVED ISONIAZID
FOR TUBERCULOSIS PREVENTION IN INJECTION DRUG USERS**

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Abstract

Substance abuse is associated with high risk for tuberculosis (TB) and poor adherence to medication regimens. This study compared completion rates for isoniazid (INH) preventive therapy for injection drug users randomly assigned to methadone treatment combined with directly observed preventive treatment (DOPT) vs those assigned to routine TB clinic referral without methadone treatment. 111 opioid-dependent patients with latent tuberculosis were assigned to one of three 6-month treatment conditions: standard methadone treatment including substance abuse counseling combined with daily INH DOPT (n = 37); minimal methadone treatment without counseling, also combined with daily INH DOPT (n = 35); or routine care referral to TB clinic for monthly INH supplies without DOPT and without methadone treatment (n = 39). INH completion rates were 77.1% for minimal methadone and 59.5% for standard methadone, as compared to only 13.5% for routine care ($p < .0001$). Mean duration of INH treatment retention was 5.0, 5.7 and 1.6 months, respectively ($\chi^2_{LR} = 74.5, df=2, p < .0001$). TB incidence at 4-year follow-up was 0 of 54 subjects who completed preventive therapy versus 2 of 57 who failed to complete. In conclusion, INH retention time and completion rates were significantly improved by methadone treatment combined with observed INH, whether or not substance abuse counseling was provided.

1. Introduction

While the tuberculosis (TB) epidemic has responded to aggressive prevention and treatment efforts (McKenna et al., 1998), TB continues to be a serious problem. Individuals with substance use disorders, including injection drug users (IDUs), are at particularly high risk. Two major TB risk factors, infection with human immunodeficiency virus (HIV) and homelessness, converge in IDUs and contribute to the high incidence of TB infection in these patients (Reichman et al., 1979; Selwyn et al., 1989; Centers for Disease Control and Prevention (CDC), 1995a; Rusen et al., 1999). Risk is even higher among those IDUs who belong to ethnic minority groups and who are indigent (Friedman et al., 1987; Snider and Hutton, 1989; Daley et al., 1992). Tuberculin skin test conversion incidence is as high as 3% per year, even among treatment IDUs (Durante et al., 1998). In addition to having higher rates of latent TB infection, IDUs are also at greater risk for progression to active TB (Perlman et al., 1995).

Preventive therapy for latent infection is essential to the control of TB and can prevent development of active disease among tuberculin positive individuals (American Thoracic Society, 1992). A commonly used chemoprophylaxis regimen is 6 months of isoniazid (INH), which decreases occurrence of active TB by 60-90% (Ferebee, 1970; Comstock and Woolpert, 1984; Centers for Disease Control and Prevention (CDC), 1990; Pape et al., 1993) and was at the time of this study the preventive therapy recommended by the American Thoracic Society and the Centers for Disease Control and Prevention (Bass et al., 1994). If, however, patients do not complete preventive therapy, they derive less benefit and develop TB at a higher rate (Gourevitch et al., 1998). Chemoprophylaxis completion rates are frequently low; only about half of patients complete the 6-month course (Centers for Disease Control and Prevention (CDC), 1995b). Furthermore, patients with substance use disorders are more likely to miss doses of self-administered TB medications than other TB clinic patients (Combs et al., 1990).

Direct observation of preventive therapy (DOPT) is a technique to improve TB chemoprophylaxis completion rates, yet it may be difficult to provide to high-risk groups such as drug users. For example, only 49% of men in a homeless shelter completed twice weekly INH DOPT (Nazar-Stewart and Nolan, 1992). Even among drug users in residential treatment, DOPT was completed by less than 50% of patients (Foley et al., 1995). Similarly, while directly observed therapy (DOT) for active

tuberculosis has yielded high completion rates in previously noncompliant patients, (McDonald et al., 1982) completion of DOT is less likely among substance users (Burman et al., 1997; Perlman et al., 1997), including IDUs (Pablos-Maendez et al., 1997; Marco et al., 1998;). In a Spanish study of TB treatment that required only twice weekly visits, injection drug use was the main predictor of noncompletion (Caminero et al., 1996).

DOPT with IDUs may be more feasible if conducted in settings that patients already attend on an ongoing basis, such as methadone maintenance programs (Centers for Disease Control and Prevention (CDC), 1995a; Centers for Disease Control and Prevention (CDC), 1999). While DOPT is provided in some methadone treatment programs, such services are not universally available. Methadone programs have been shown to be an effective platform for the delivery of a number of health services including primary medical care for conditions such as active TB (Marco et al., 1998; Elk et al., 1993), and HIV disease (Batki, 1988; Selwyn et al., 1989; Sorensen, 1991; Goosby et al., 1992; Selwyn et al., 1993; Umbricht-Schneiter et al., 1994; Selwyn, 1996). Because methadone programs treat large numbers of at-risk patients who attend the clinic daily or almost daily, they are a logical nexus for providing tuberculosis prevention services (Brown and Felton, 1989; Haverkos and Lange, 1990). A randomized trial studying the impact of location of tuberculosis screening showed that chest radiograph completion by drug users was much higher in a methadone clinic than in a nearby medical clinic (86% vs. 23%) (Umbricht-Schneiter et al., 1994). Completion rates for directly observed INH have been as high as 80-90% in methadone programs (O'Connor et al., 1992; Gourevitch et al., 1998; Snyder et al., 1999), regardless of participants' drug use (Gourevitch et al., 1996). This contrasts with other settings, where TB medication adherence among substance users has been lower than among non-users (Combs et al., 1990), even with direct observation (Burman et al., 1997; Pablos-Maendez et al., 1997; Perlman et al., 1997). Completion rates are higher in methadone treatment than the average of 66% found in other types of drug treatment settings (Centers for Disease Control and Prevention, 1993). However, to date there have been no reports of controlled trials to demonstrate that DOPT in methadone programs actually increases completion rates over routine provision of TB preventive therapy without methadone.

Given the high risk and serious public health consequences of incomplete preventive therapy among IDUs, clinical trials are needed to measure the impact of interventions to improve completion rates. The present study is a controlled trial of 6 months of methadone treatment – both with and without substance abuse counseling – combined with directly observed INH, as compared to routine referral to tuberculosis clinic to receive monthly INH supplies without direct observation of medication ingestion and without methadone treatment.

2. Methods

2.1. Participants

Heroin dependent IDUs entering the 21-day methadone detoxification clinic at San Francisco General Hospital (SFGH) received medical examination including tuberculin skin testing with purified protein derivative (PPD) at admission. Skin tests were read by registered nurses 48-72 hours after placement. Patients with positive PPDs received chest radiographs. From March 1995 through December 1996, tuberculin positive patients with negative chest radiograph who met the inclusion criteria were invited by the clinic's tuberculosis nurse to participate in the study (Figure 1: Subject Flow Diagram).

To participate in the study, patients had to meet the following inclusion criteria: 1) latent tuberculosis infection as demonstrated by a positive PPD test (10 mm or greater in duration), a negative chest radiograph, and approval by a tuberculosis clinic physician; 2) a DSM-III-R diagnosis of opioid dependence; 3) age between 21 and 59 years; 4) expressed willingness to receive 6 months of INH preventive therapy and methadone treatment. Patients could not participate if they were: 1) pregnant (pregnant patients were immediately admitted to the regular methadone maintenance program), 2) HIV positive (also immediately admitted to methadone maintenance), or 3) had evidence of active liver disease or aspartate transaminase (AST) greater than three times the upper limit of the normal range.

Patients who were eligible for the study underwent complete informed consent procedures, as approved by the University of California San Francisco Institutional Review Board. This included description of study procedures, risks and benefits, payment, and participant rights, all of which followed the international standards for human experimentation. These were presented in writing and in person. Subjects signed and received copies of the consent form and a research subject bill of rights. A Federal Certificate of Confidentiality was obtained to further protect participants' confidentiality.

Of the 115 individuals who were eligible and who consented to participate in the study, 4 subjects were excluded prior to completion of the baseline assessments and before treatment was started (during assessment, 1 was found to have past history of INH intolerance, 2 were judged to have active TB, and 1 dropped out). Table 1 summarizes the characteristics of the 111 randomized study participants. The schedule for randomization to treatment condition was generated by a statistician who placed subject assignments in individual sealed envelopes and did not reveal the schedule to project staff. At the conclusion of each intake interview, the project staff opened the envelope, which contained the condition assignment.

The 111 participants entered one of the 3 randomly assigned levels of care: 37 were assigned to Standard Methadone Treatment (Standard MT) -- with substance abuse counseling plus directly observed daily INH; 35 to Minimal Methadone Treatment (Minimal MT) -- without counseling, also with directly observed INH; and 39 to Routine Care -- consisting of no methadone treatment, only referral to the adjacent Tuberculosis Clinic for monthly visits for 30-day supplies of INH and with no direct observation of medication ingestion.

The Routine Care condition was the usual level of care available to out-of-treatment HIV seronegative heroin dependent patients because of the severe shortage of methadone maintenance treatment slots in San Francisco at the time of the study. For example, in 1996 there were 1613 methadone maintenance treatment slots in the city, while there were an estimated 14,900 heroin users (Newmeyer, 1988; Meredith et al., 1996). This research study created additional no-cost 6-month methadone treatment slots.

2.2. Treatment Conditions

Standard Methadone Treatment, (modeled after McLellan et al., 1993): Participants in the Standard MT group received DOPT in the form of daily observed doses of INH (300 mg) and pyridoxine (50 mg) in addition to daily methadone doses in the 60-90 mg range, 7 days per week for 6 months, followed by a 6 week taper off methadone. They also received twice monthly counseling sessions, weekly random observed urine samples, medical services, psychiatric treatment as needed, and social work referrals. This differed somewhat from the McLellan et al. (1993) Standard MT protocol in which counseling was provided weekly, but no medical, psychiatric, or social work services were offered. Similar to McLellan et al. (1993), participants could earn up to two take-home doses of methadone per week as a reward for negative urine drug and breath alcohol tests. However, no participants actually earned take-home doses.

Minimal Methadone Treatment (modeled after McLellan et al., 1993): Participants in the Minimal MT group also received DOPT in the form of daily observed doses of INH and pyridoxine as well as daily methadone doses in the 60-90 mg range, 7 days per week for 6 months, followed by a 6 week taper off methadone. They received no counseling or any other services, except on an emergency basis or to enforce program rules. As a result, counselor contacts with participants were infrequent (approximately once per month, for no more than 15 minutes). Counselors and clients were not informed of urine or breathalyzer test results. No take-home doses of methadone could be earned, in contrast to the treatment of McLellan et al. (1993). The level of care in the Minimal MT condition approximated the "Interim Maintenance Treatment" guidelines under current Federal guidelines (FDA, 1994).

Routine Care: The routine care control group consisted of standard referral to the San Francisco county Tuberculosis Clinic -- located in the same hospital building as the methadone clinic-- for a 6-month course of INH preventive therapy. This consisted of six monthly appointments in the Tuberculosis Clinic to receive six 30-day supplies of INH and pyridoxine, but without DOPT -- they received no daily direct observation of medication ingestion. In keeping with the standard care available to out-of-treatment HIV antibody-negative IDUs in San Francisco at the time of the study, they were also eligible for readmission to another 21-day detoxification episode seven weeks after the original admission. Routine Care subjects could also seek methadone maintenance treatment elsewhere. In fact, 7 participants in the Routine Care

group did enter methadone treatment elsewhere while in the study. All remained included in the analyses reported below.

2. 3. Measures

Pre-treatment measures: Normal clinical admission procedures at the SFGH methadone detoxification clinic included a medical examination and tuberculin skin testing, HIV and Hepatitis B antibody testing, VDRL, blood count, chemistry panel, and urine pregnancy test. For tuberculin positive patients, a chest radiograph was obtained and reviewed by a tuberculosis clinic physician. A urine drug test (PathLab., San Jose, CA) employing thin layer chromatography screening and high performance liquid chromatography confirmation was done at admission. Computerized methadone registration checks ensured that patients were not simultaneously receiving treatment elsewhere in the San Francisco area. After study entry, demographic information was obtained and the Structured Clinical Interview for DSM-III-R (SCID) (Spitzer et al., 1989) was administered.

Measures administered at baseline and monthly: All participants were asked to complete interviews and provide urine specimens at baseline and at each of the 7 monthly follow-ups. They were paid \$12 for each completed interview. These unobserved urine samples were in addition to weekly random samples collected in the Standard MT and Minimal MT conditions. Urine was analyzed for the heroin, methadone, cocaine, amphetamines, barbiturates, benzodiazepines, and phencyclidine. Self-report of heroin and cocaine use in the past week was obtained with the Quantitative Drug Inventory (Gawin and Kleber, 1984). The Addiction Severity Index (ASI), 5th edition (McLellan et al., 1992b) was used to assess addiction problem severity in the past 30 days. The Risk for AIDS-related Behaviors (RAB) (Metzger et al., 1993) was used to assess sexual and drug use behaviors related to HIV infection. The Beck Depression Inventory (BDI) (Beck et al., 1961) was also administered monthly. Monthly INH toxicity symptoms (Drug Toxicity Monitoring Guide, Tuberculosis Clinic, Department of Public Health, San Francisco), and monthly aspartate transaminase levels were obtained to monitor for adverse effects of INH. The Treatment Services Review (TSR) (McLellan et al., 1992a) was used to assess treatment services received in the past week.

The TSR asked about services received both within the methadone treatment program (if applicable) and elsewhere.

Tuberculosis chemoprophylaxis medication adherence: The primary outcome measure in this study was the proportion of participants in each condition who completed a six-month course of tuberculosis preventive therapy (defined as 80% or more of doses taken). A related outcome was the number of months chemoprophylaxis was taken as prescribed. For the MT groups, this was measured by nurses' attendance and medication records. For the Routine Care group, this was measured using TB clinic medication records that documented monthly pick-up of INH/pyridoxine supplies.

Active TB cases: The incidence of active TB in each of the 3 groups was assessed through March 2000, an average of 4 years after study entry, by review of the San Francisco Tuberculosis Control records. Active TB was defined according to the usual clinical criteria employed by the agency.

2. 4. Statistical Analysis

All analyses were intent-to-treat analyses, including the primary outcome of INH completion.

Participant characteristics: The three study groups were analyzed for differences in demographic, drug use, and psychiatric characteristics using one-way analyses of variance and Pearson chi-square tests.

Treatment Services Review: **KEVIN: THIS SECTION SEEMS CONTRADICTIONARY. DID WE DO THIS TEST?** Repeated measures Kruskal-Wallis test was used to analyze for differences among the three groups in the amount and types of services received during the week prior to each interview. These analyses were conducted to show whether the treatment groups received different levels of service, as intended. **KEVIN: OR DID WE DO THIS TEST?** One-way ANOVAs were also used to compare the amount and types of treatment services received during the week prior to each interview to test whether the treatment groups received different levels of service as intended. **TABLE 2 MENTIONS KRUSKAL-WILCOXIN TEST. SHOULD THAT BE MENTIONED HERE?**

Completion of tuberculosis preventive therapy: The proportions of participants completing the 6-month course of INH were compared across the three study groups using a Pearson chi-square statistic.

Duration of INH and methadone treatment: **KEVIN: MORE CONTRADICTIONARY SENTENCES ABOUT DIFFERENT TESTS - WHICH TEST WAS USED?** The logrank chi-square Wilcoxon test

KEVIN: OR WAS IT Kruskal-Wallis one-way nonparametric test was used to compare duration of INH treatment for all 3 groups, and methadone treatment for each of the 2 methadone treatment groups.

KEVIN, THIS REPETITION OF THE ABOVE HAS DIFFERENT TESTS – WHICH ONE WAS IT? COULD THIS BE CUT? Number of months of treatment for the three groups -- Standard MT, Minimal MT, and RC -- was compared using the Kruskal-Wallis one-way non-parametric test. For the two MT groups, number of days for INH dosing were analyzed using a t-test.

Correlates of treatment completion: Pearson correlation coefficients and coefficients with the effects of treatment condition partialled out were used to test for relationships among intake measures and the outcome measures, completion status and duration of INH dosing.

3KEVIN: JAMA CHECKLIST #7 REQUIRES RATIONALE FOR THE STATISTICS SELECTED.

. Results

3. 1. Participant Characteristics

Table 1 shows the characteristics of participants. There were significant differences between the three groups on the following variables: age ($p = .047$), ASI psychiatric composite score ($p=.027$) and BDI scores ($p=.022$). Both ASI psychiatric composite and BDI were lowest in the Minimal MT condition and highest in the Routine Care group.

3. 2. Services Received

Treatment service use in the week prior to an assessment, as measured by the TSR, was compared among study conditions at baseline, three, and six months, using the Kruskal-Wallis test. Services received outside of the study were compared among all three conditions, and those received as part of the study were compared between the two methadone conditions only.

Median number of services used was zero for virtually all TSR categories at all timepoints. For the "out-of-treatment services," no differences were found at baseline. A clear pattern of differences, however, was found at Month 3, consisting of a significantly greater outside services received by the Routine Care group (see Table 2). At Month 6, only the medical services showed a significant difference with more Routine Care participants receiving outside medical services than either of the methadone treatment

conditions. No differences in services were found between the two methadone treatment conditions in any category at any assessment point.

3. 3.

INH Preventive Therapy Completion

INH completion was defined as 80% or greater of all doses taken (at least 144 of 180 possible doses). An intent-to-treat analysis was applied, in which all of the subjects assigned to the Routine Care group were included. INH preventive therapy was completed by 22 subjects (59.5%; CI 43.6 - 75.3) in Standard Methadone Treatment, 27 (77.1%; CI 61.3 - 91.0) in Minimal Methadone Treatment, and 5 (13.1%; CI 3 - 23.7) in Routine Care. Of the 5 TB preventive therapy completers in the Routine Care group, 2 (40%) had been admitted to methadone maintenance treatment elsewhere and had received daily observed INH outside of the study.

The two methadone treatment groups had significantly higher INH completion rates compared to the Routine Care group (Pearson chi-square=33.1 (1), $p < .0001$). There was no significant difference between the two methadone groups in the rate of INH completion.

Noncompletion in the two methadone groups was due to nonattendance at clinic in 5 (33%) of the Standard MT noncompleters and 3 (37.5%) of the Minimal MT noncompleters. Withholding of INH due to adverse effects was the reason in 4 (27%) of the Standard MT and 3 (37.5%) of the Minimal MT noncompleters. The most common reasons for noncompletion in the Routine Care group were failure to pick up the the initial supply of INH, in 16 (47%) of the noncompleters, and failure to return for subsequent monthly INH supplies in 8 (23.5%).

3. 4. Duration of INH preventive therapy

INH preventive treatment retention time was significantly different among treatment groups, with those participants who received methadone treatment staying longer than the Routine Care group. Mean INH treatment retention was 5.0 months (CI: 4.5 - 5.5) for the Standard MT group, 5.7 months (CI: 5.4 - 6.0) for the Minimal MT group, and 1.6 months (CI: 0.9 - 2.25) for the Routine Care group ($\chi^2_{LR} = 74.5$,

df=2, $p < .0001$). Duration of INH did not differ significantly between the two methadone groups (21.6 [CI: 19.4 - 23.9] weeks for the Standard MT group and 24.6 [CI: 23.2 - 25.9] for the Minimal MT group, ($\chi^2_{LR} = 1.70$, df=1, $p = .1924$). Survival curves for retention for all three groups are shown in Figure 2. The majority of subjects in the two methadone groups remained in preventive treatment for 6 months. In contrast, in the routine care group, only 41% of patients did not even pick up their first month's supply of INH at the TB clinic, and only a fraction remained in treatment for 6 months.

3. 5.

Adverse effects

Adverse effects for 13 subjects in the two methadone groups led to temporary discontinuation of INH due to elevations in AST levels. These subjects' AST elevations during treatment were judged to be possibly INH-related. All 13 were re-challenged with INH following the advice of the Tuberculosis Clinic physicians. All but 5 were able to resume and continue INH treatment.

3. 6.

Active Tuberculosis Cases

At follow-up -- on average 4 years after study entry -- 2 (3.5%) of the 57 noncompleters, but none of the 54 completers had been diagnosed with active TB according to San Francisco Department of Public Health TB Clinic records. Of the noncompleters, 1 had been assigned to routine care, and 1 had been assigned to Minimal MT.

3. 7. *Predictors of Completion:*

We examined the relationships between several potential predictive variables assessed at intake and two outcome measures -- completion of INH treatment (for all 3 groups) and the number of days of INH received (for the two groups in methadone treatment only -- daily INH data was not obtainable for the Routine Care condition). Potential predictors included current diagnosis of alcohol abuse or dependence and the number of days of alcohol use in the past 30 days, current cocaine abuse or dependence, stated level of commitment to abstinence as a treatment goal, urine test results, ASI psychiatric severity, BDI score, diagnosis of antisocial personality disorder, homelessness, ethnicity, and gender.

None of the candidate variables was significantly related to completion of INH treatment. However, one of the measures -- diagnosis of current major depression -- was significantly related to number of days of INH treatment in the two methadone treatment groups. Participants who entered the study with major depressive disorder received fewer daily doses of INH (mean = 119.4, sd = 47.46) than those without this diagnosis (N=57, mean = 146.1, sd = 35.93; $t=2.27$, $p = .026$). Although depression was less common in the Minimal MT condition than in Standard MT, this relationship **was significant within each treatment group (KEVIN: CAN WE SAY IT'S SIGNIFICANT WITHIN TREATMENT GROUPS, AS REQUIRED BY JAMA CHECKLIST # 18? WHAT WAS PREVIOUSLY WRITTEN HERE WAS: remained significant when treatment condition was controlled for statistically.)**.

4. Discussion

This is the first reported controlled trial for improving the completion rates for TB preventive treatment by providing methadone treatment with directly observed TB preventive therapy, as compared to routine monthly INH prescriptions without methadone treatment. These out-of-treatment-treatment opiate-dependent subjects were randomly assigned to methadone treatment with or without counseling, or to routine care.

The trial demonstrated several findings. First, methadone treatment was associated with a robust increase in completion rates. INH completion was much higher for the two methadone groups (59.5% and 77.1%) than for the routine care group (13.1%). The second major finding was that methadone treatment was associated with an increase in duration of TB preventive therapy. Mean retention was 5 months in the methadone groups, in contrast to less than 2 months in the routine care group -- a duration with close to zero effectiveness (International Union Against Tuberculosis Committee on Prophylaxis, 1982). The low TB clinic adherence rate to first and subsequent visits at the TB clinic occurred even though that clinic was in the same building as, and only one floor above, the methadone clinic from where patients were referred.

Third, the beneficial effects of methadone treatment on completion of preventive therapy were not improved by the provision of substance abuse counseling, but instead appeared to be related solely to the daily clinic attendance for methadone and INH dosing. In contrast, in a similar study of six-month methadone treatment by McLellan et al. (1993), ongoing substance abuse counseling resulted in more drug free urine samples than did minimal counseling. Fourth, at an average 4 year follow-up, 2 of the INH noncompleters had developed active TB, as compared to none of the completers.

Fifth, in order to identify who was most and least likely to complete INH chemoprophylaxis, the study evaluated several drug use, psychiatric, and psychosocial variables as possible predictors of completion (Burman et al., 1997; Pablos-Maendez et al., 1997; Tulsy et al., 2000). Drug use did not predict completion, consistent with the findings of Tulsy et al. (2000) and Gourevitch et al. (1996). However, within the two groups assigned to methadone treatment, participants who met criteria for Major Depression had fewer days of INH taken. This association is consistent with previous research showing depression to be linked to lower medication adherence, such as to medications for HIV disease (Gordillo et al., 1999; Catz et al., 2000), and to cardiovascular medications among patients with coronary artery disease (Carney et al., 1995).

Even with daily provision of methadone and INH, a substantial proportion of the methadone treatment groups still failed to complete TB preventive therapy. The most common reasons for noncompletion were nonattendance and physician-initiated discontinuation of INH due to possible adverse effects. Because of the daily contact provided by methadone treatment with DOPT, there was greater opportunity to observe INH related or other adverse effects in the two methadone treatment groups. Yet despite more frequently observed adverse effects and resultant physician-initiated discontinuation, the methadone groups were still more likely to complete INH preventive therapy than the routine care group. The most common reasons for noncompletion in the routine care group were failure to pick up the initial INH supply from TB clinic and failure to return for subsequent months' supplies. It is also possible that patients in routine care group had unobserved INH toxicity and stopped taking the medication on their own due to adverse effects.

INH completion rates, particularly in the routine care group, were lower in this study than in other studies. INH completion in the routine care group was 13.1%, even lower than the 26% found among

homeless clients at the same TB clinic by Tulskey et al. (2000). Likewise, INH completion rates in the methadone groups were lower than in uncontrolled studies in methadone maintenance clinics that reported completion rates of 80-90% (Gourevitch et al., 1996; Gourevitch et al., 1998; Snyder et al., 1999). Random assignment in our study eliminated any possible assignment bias in entering patients into methadone treatment, and may have resulted in a cohort of methadone patients who differed in a number of ways from patients in other studies. First, subjects in our cohort may have had more complex substance abuse, medical, psychiatric, and psychosocial problems than those in other studies. All were indigent patients referred from the county hospital inpatient medical or psychiatric units for outpatient methadone detoxification. Most were homeless or had unstable housing. Second, in contrast to other studies of DOPT in methadone maintenance programs, subjects had been out of treatment until just before the study, and had just recently entered a short-term treatment -- 21-day methadone detoxification. Third, the methadone treatment offered to the Standard-MT and Minimal-MT groups was limited to only six months, while in other studies patients were in ongoing methadone maintenance, potentially continuing for many years. Therefore, patients in other studies were more likely to be stabilized and able to attend the clinic regularly for directly observed methadone and INH dosing. Fourth, in the present study, most methadone patients discontinued INH one month before the end of their six-month methadone treatment. The most common reason for INH discontinuation in the methadone groups was dropout from methadone treatment. The anticipated end of methadone treatment could have been a destabilizing influence contributing to dropout from shortly before the planned termination.

The most significant limitation of the study was the lack of a treatment condition that would have provided observed INH administration *without* methadone treatment. Such a condition would have allowed evaluation of the relative impact on adherence of either methadone alone or observed INH administration alone. It is possible that most of the effect is attributable to observed INH dosing. Findings from this study and that of Tulskey provide further support for the feasibility and efficacy of DOPT in hard-to-reach populations such as drug users if participants are given an incentive to attend the setting where therapy can be observed (the incentive was methadone in the present study and cash in the Tulskey study).

Methadone treatment appears to have the role of creating the conditions in which DOPT will be successful, by motivating patients to attend daily for observed treatment.

Some limitations may affect interpretation of the results. Our study was based on a daily INH dose paradigm, and completion rates may be different for newer methods of providing TB preventive medications with less frequent dosing (Graham et al., 1996), or shorter duration requirements (Gordin et al., 2000). Another significant limitation was the need to exclude HIV seropositive IDUs because the standard of care at the time of this study was to preferentially admit them to methadone treatment. IDUs with HIV disease may be different from our cohort in a number of ways that may limit the generalizability of our findings. Despite the limitations, the strengths in study design result in a high likelihood that the conclusions drawn above are valid. In this randomized clinical trial, it is unlikely that differences in participant characteristics could explain the differences in outcomes.

The findings of this study suggest several directions for future investigation. Further research is necessary to assess the precise value of methadone versus other potential incentives for daily attendance for observed treatment. Next steps in this line of research should include testing DOPT with methadone versus DOPT without methadone, but with other attached incentives such as vouchers for goods and services, versus DOPT alone. Effects of these interventions need to be evaluated using TB preventive medications with less frequent or lengthy dosing requirements. Also, cost effectiveness of methadone and DOPT remains to be determined through research designed specifically to measure that outcome.

In conclusion, the significantly enhanced adherence to, and completion of, TB preventive therapy that was seen in the subjects assigned to methadone treatment and DOPT is further evidence for the utility of methadone treatment programs in providing stable settings, or “platforms” for the provision of medical and public health interventions. Our findings give strong support to health care policy changes that would seek to increase the availability of methadone treatment. Such treatment – with or without substance abuse counseling – could be particularly useful in the care of drug users with medical problems such as HIV, tuberculosis, Hepatitis C, and other conditions requiring intensive, complex, or lengthy medical treatments.

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TABLE 1
Participant Characteristics

		% (n)			p-value
		Standard Methadone Treatment	Minimal Methadone Treatment	Routine Care	
Gender:	Male	54% (20)	54% (19)	74% (29)	
	Female	46% (17)	46% (16)	26% (10)	
Pearson's chi-square = 4.35, p value = .114					
Ethnicity:	African American	30% (11)	34% (12)	27% (10)	
	White	46% (17)	37% (13)	40.5% (15)	
	Other	24% (9)	29% (10)	32.5% (12)	
Pearson's chi-square = 1.09, p value = .896					
Marital Status:	Married	29.4% (5)	41.2% (7)	29.4% (5)	
	Widowed	40% (2)	20% (1)	40% (2)	
	Separated	50% (8)	18.8% (3)	31.3% (5)	
	Divorced	27.8% (10)	36.1% (13)	36.1% (13)	
	Never Married	33.3% (12)	27.8% (10)	38.9% (14)	
Pearson's chi-square = 4.17, p value = .842					
Current Major Depression		34.8%	21.7%	43.5%	.518
Opioid Dependence		100%	100%	100%	-
Alcohol Abuse		21.6%	12.1%	18%	.568
Alcohol Dependence		16.2%	12.1%	7.7%	.532
Cocaine Abuse/Dependence		48.6%	42.4%	41.0%	.780
Goal To Quit Heroin Completely (%)		35.1%	25.7%	46.5%	.186

TABLE 1
Participant Characteristics (cont.)

	Mean (S.D.)			p-value
	Standard Methadone Treatment	Minimal Methadone Treatment	Routine Care	
Age (yrs)	40.2 (4.8)	42.6 (6.2)	43 (4.8)	.047
Education	12.0 (2.3)	11.9 (2.0)	12.2 (1.6)	.79
Income (per month)	\$1,262 (1,461)	\$1,308 (1,853)	\$1,608 (1,853)	.64
Years of Heroin Use	14.5 (88.1)	19.1 (80.5)	0 (0)	.448
RAB Drug Risk	5.32 (6.98)	6.34 (7.29)	5.87 (6.77)	.827
RAB Sex Risk	2.84 (3.32)	3.23 (3.70)	2.10 (2.82)	.326
ASI: Medical	.44 (.35)	.32 (.36)	.45 (.40)	.277
Employment	.79 (.25)	.86 (.23)	.80 (.25)	.506
Alcohol	.07 (.06)	.07 (.10)	.09 (.14)	.618
Drug	.74 (1.2)	.50 (.76)	.50 (.63)	.409
Legal	.21 (.24)	.21 (.23)	.31 (.27)	.186
Family	.25 (.16)	.24 (.16)	.21 (.18)	.661
Psychiatric	.23 (.26)	.14 (.18)	.30 (.24)	.027
Beck Depression Inventory	16.4 (9.03)	13.7 (9.81)	20.2 (11.12)	.022

Table 2. Percent of participants reporting no treatment services outside of study-supplied services at Month 3 based on TSR categories.

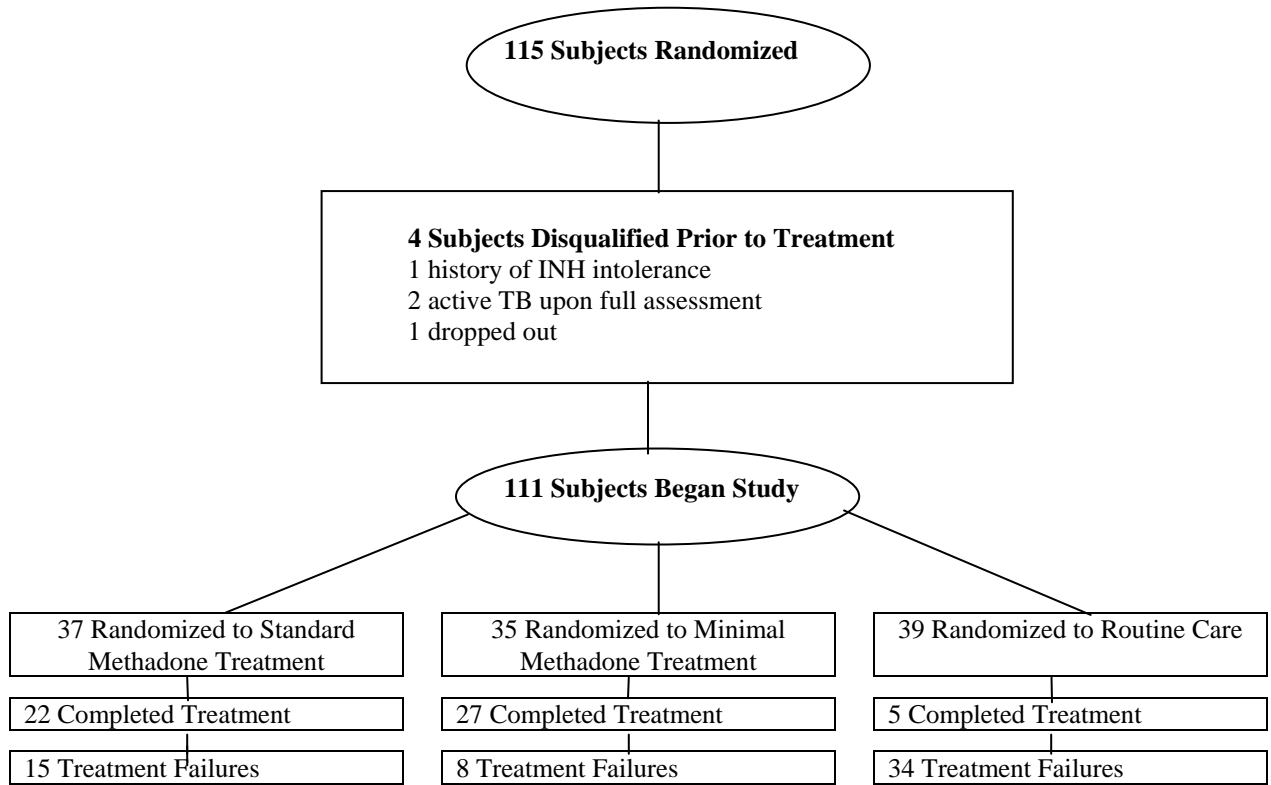
TSR Category	Standard Methadone Treatment	Minimal Methadone Treatment	Routine Care	p-value*
Medical	87.5	80.8	44.4	.005
Employment	73.3	87.9	61.5	.064
Alcohol	93.3	90.9	73.1	.059
Drug	86.7	90.9	53.8	.001
Legal	96.7	87.9	69.2	.016
Family	96.7	93.9	96.1	.859
Psychological	96.7	97.0	84.6	.111

* P-values from Kruskal-Wallis test of number of services reported as used in prior 7 days.

Legend for Figure 1:

Fig. 1. Subject flow diagram, indicating assignment of subjects to the 3 treatment conditions.

SUBJECT FLOW DIAGRAM



Legend for Figure 2:

Fig. 2. Proportion of participants retained in INH preventive therapy, by months retained in treatment. Mean treatment retention time differed significantly in the treatment groups

($\chi^2_{LR} = 74.5$, $df=2$, $p < .0001$).

- **Standard MT: 6 months of methadone treatment with substance abuse counseling and combined with daily observed preventive therapy (DOPT) with INH.**
- **Minimal MT: 6 months of methadone treatment with no substance abuse counseling; also combined with DOPT with INH.**
- **Routine Care: Routine referral to Tuberculosis Clinic for a 6 month course of monthly dispensed supplies of INH, without DOPT and without methadone treatment provision.**

Retention in INH Preventive Therapy

