REVIEW ARTICLE

Tuberculosis and Illicit Drug Use: Review and Update

Robert G. Deiss, Timothy C. Rodwell, and Richard S. Garfein

University of California, San Diego, and Department of Family and Preventive Medicine, Division of International Health and Cross-Cultural Medicine, La Jolla, California

Illicit drug users continue to be a group at high risk for tuberculosis (TB). Here, we present an updated review of the relationship between TB and illicit drug use, and we summarize more than a decade of new research. Drug users, and injection drug users in particular, have driven TB epidemics in a number of countries. The successful identification and treatment of TB among illicit drug users remain important components of a comprehensive TB strategy, but illicit drug users present a unique set of challenges for TB diagnosis and control. New diagnostic modalities, including interferon-γ–release assays, offer potential for improved diagnosis and surveillance among this group, along with proven treatment strategies that incorporate the use of directly observed therapy with treatment for drug abuse. Special considerations, including coinfection with viral hepatitis and the rifampin-methadone drug interaction, warrant clinical attention and are also updated here.

INTRODUCTION

Illicit drug use (hereafter, "drug use") and injection drug use are important factors in the epidemiology of tuberculosis (TB) in developed and developing countries [1–8]. Although the incidence of TB in most industrialized nations has decreased over the past decade, the burden of disease is being increasingly borne by urban subpopulations, including drug users. Recognizing the important relationship between TB and drug use, the World Health Organization, the Joint United Nations Programme on HIV/AIDS, and the United Nations Office on Drugs and Crime recently issued a set of guidelines to better coordinate care for TB among drug users [9]. A comprehensive literature review, however, has not been published since 1995 [10], although a number of studies have since proposed new approaches to the diagnosis and treatment of TB in this group at high risk. In this review, we provide clinicians and public health practitioners with an outline of special considerations and the latest evidence concerning TB management among drug-using populations.

In preparing this review, we comprehensively searched the MedLine database (1995–2008) using terms that included TB, injection drug use, drug use, and substance abuse. Articles in English and Spanish were selected for full-text review. We also reviewed the reference lists of those articles and included additional manuscripts that were of historical significance. As noted in a prior review [10], the distinction between the terms "drug use" and "injection drug use" is not always clear in the TB literature. In this review, the broader term "drug use" is used unless we refer to a study that specified "injection drug users" (IDUs) as its exclusive study population. Overlap between these groups is not expected to be methodologically important, because studies comparing TB among IDUs with TB among non-IDUs have not found consistent and important differences (see below).

TB RISK AND PREVALENCE AMONG DRUG USERS

Drug use has been associated with a higher prevalence of latent TB infection (LTBI) [11, 12] and incidence of

Received 18 March 2008; accepted 16 September 2008; electronically published 1 December 2008.

Reprints or correspondence: Dr. Richard S. Garfein, University of California, San Diego School of Medicine, Div. of International Health and Cross-Cultural Medicine, 9500 Gilman Dr., MC 0622, La Jolla, CA 92093 (rgarfein@ucsd.edu).

Clinical Infectious Diseases 2009; 48:72–82

1058-4838/2009/4801-0011$15.00
DOI: 10.1086/594126

TB disease [13, 14]. A number of studies [15–36] have characterized the LTBI prevalence (10%–59%) among various cohorts of drug users (table 1). In these studies, duration of injection drug use and older age were most commonly associated with LTBI. Studies comparing the prevalence of LTBI among IDUs with that among non-IDUs have yielded mixed results [15, 20, 21, 23, 25, 29, 31], which indicates that these groups share a similar risk of LTBI.

The physiological effects of drug use, along with the environment and risk behaviors of drug users, may all contribute to the high prevalence of TB among drug users. A number of in vitro studies have demonstrated deleterious effects of drug use on the immune system [37], with biologic evidence supporting direct impairment by opiates of the cell-mediated immune response [38]. Although the clinical implications of this evidence remain unclear [39], drug use is frequently associated with a number of epidemiological factors, including tobacco use, homelessness, alcohol abuse, and incarceration, that confer additional risk of TB [40–45]. Together, these physiological and epidemiological factors may contribute to observed outcomes—namely, that drug users are more likely to be infectious [8, 46, 47], to take longer to achieve negative culture [47, 48], and to be at increased risk of mortality [49, 50].

The high prevalence of LTBI and longer periods of infectivity may further contribute to increased rates of TB transmission among drug users. Evidence from contact investigations [51, 52] and molecular epidemiological studies [6, 53–59] demonstrates that a disproportionate incidence of TB disease among drug users results from TB transmission, and the presence of identical DNA patterns ("clusters") in TB isolates implies recent transmission [60]. Cluster analysis has been used to identify outbreaks of drug-resistant TB among drug users in England [8] and multidrug-resistant TB in Thailand [2], Argentina [61], Latvia [62], and Portugal [63]. In the United States, a TB outbreak occurred at a methadone-treatment facility [64], and 1 patient subsequently became the source case for a hospital outbreak of multidrug-resistant TB [65]. TB outbreaks among non-IDUs have also been attributed to sharing drug equipment or to cramped conditions and poor ventilation [66–70]. "Shotgunning," a practice of inhaling and then exhaling smoke (e.g., crack cocaine or hashish) directly into another's mouth, has been reported among 17% [71] and 62% [72] of drug users and was implicated in a South Dakota TB outbreak [73].

Although drug use was described as a TB risk factor even before the HIV era [74], HIV-induced immunosuppression is the most important reason for the high TB incidence among IDUs [75]. Most available evidence (table 2) demonstrates that HIV-infected IDUs are at greater risk of TB infection [11] and disease [76–85], compared with other HIV-infected individuals, although this is sometimes confounded by regional or ethnic factors [77, 86–88]. High prevalence of TB coinfection is commonly reported among HIV-positive IDUs [89, 90], particularly those in prison [43, 91, 92]. TB is often the most common opportunistic infection in areas of TB endemicity [77, 93, 94], and it is also seen among IDUs even in areas of low prevalence of TB [86]. Risk of TB disease among IDUs has been shown to peak several years after they became infected with HIV, in both the pre-HAART [88] and the HAART eras [85]. The time immediately after diagnosis of HIV infection represents an opportunity for TB prevention and/or treatment, but important barriers remain for the care of TB among drug users.

BARRIERS TO CARE AND TREATMENT ADHERENCE

Two hallmarks of TB control are the effective identification and treatment of cases, and here, drug users present a unique set of challenges. Studies have reported that IDUs have difficulty completing medical evaluations [27, 35, 95] and/or adhering to treatment for LTBI [35] or TB disease [96]. Even symptomatic IDUs have waited to present for treatment until after TB symptom onset ("patient delay") [97], which can increase TB transmission rates and/or lead to more-severe disease [98]. Furthermore, in a study of >5000 new AIDS cases in New York City [99], patients with a history of IDU were a mean of 3.6 times more likely than other individuals with AIDS (95% CI, 1.3–10.2 times more likely) to have an opportunistic infection, including TB disease, at the time of AIDS diagnosis, further suggesting decreased care-seeking behavior among IDUs.

Although these studies demonstrate that drug users frequently delay care even when they are symptomatic, a novel hypothesis centers on whether drug users may be less aware of their TB symptoms because of opiate suppression of the cough reflex. A recent randomized, controlled trial among 27 patients with chronic cough found that patients taking 5–10 mg of morphine sulfate per day experienced a reduction in cough frequency and severity [100]. Placebo effects cannot be ruled out in any opiate trial, because patients are conscious of the effects of the drug, but the study authors found that improvement in cough symptoms was not related to the sedative properties of the opiates [100]. To our knowledge, the extent to which opiate suppression of the cough reflex may contribute to patient delay among drug users has not been studied.

Knowledge of and perceptions about TB may further impact care-seeking behavior [101]. In knowledge surveys, most IDUs understood that they were at high risk of TB [102], that HIV infection increases TB risk [103], and that TB is treatable [101, 103]. However, fewer drug users were aware that TB is spread by coughing [20, 102] or that people could become resistant to medication [102]; confusion between infection and disease is also common [20]. One study [20] reported the perception that TB can be prevented by condom use or bleaching needles, which suggests that HIV/AIDS education messages can be con-

Table 1. Summary of studies reporting prevalence of positive tuberculin skin testing (TST) among drug users, 1995–2008.

Study	Year	Location	Study subjects	No. of TST results	TST criteria	Positive TST result, %	Cutaneous anergy, %	Predictive factors	Positive for HIV infection, %
Reyes et al. [15]	1996	San Juan, Puerto Rico	716 Drug users	611	NR	10	30	Positive for HIV infection, IDU, history of incarceration, residential drug treatment	35
Converse et al. [16]	1997	Baltimore, MD	66 IDUs	NR	10 mm; 5 mm if HIV positive	30	23	NR	52
Lifson et al. [17]	1997	Denver, CO; Portland, ME; San Francisco, CA; Oakland; CA	1079 IDUs	997	10 mm; 5 mm if HIV positive	13	NR	Race/ethnicity, age group; city of residence	10
Strathdee et al. [18]	1997	Vancouver, BC	1006 IDUs	NR	NR	25	NR	NR	23
Daley et al. [19]	1998	San Francisco, CA	1109 IDUs	NR	10 mm; 5 mm if HIV positive	39	10	NR	32
Durante et al. [20]	1998	New Haven, CT	786 Drug users	662	10 mm; 5 mm if HIV positive	16	12	Older age, nonwhite ethnicity; history of IDU, foreign birth	8[a]
Malotte et al. [21]	1998	Long Beach, CA	1004 Drug users	782	5 mm	18	NR	Older age, nonwhite ethnicity, male sex	4
Robles et al. [22]	1998	San Juan, Puerto Rico	464 IDUs	424	10 mm; 5 mm if HIV positive	17	31	NR	43
Taubes et al. 23	1998	New York, NY	147 Mentally ill drug users	137	10 mm	31	NR	Recent crack cocaine use, schizophrenia	19
Alvarez Rodriguez et al. [24]	1999	Lleida, Spain	150 Drug users	NR	5 mm; 15 mm if BCG vaccinated	27	NR	History of incarceration	36
Malotte et al. [25]	1999	Long Beach, CA	1078 Drug users	777	5 mm	21	NR	History of TB exposure	3
Kimura et al. [26]	1999	Baltimore, MD	1008 IDUs	467	10 mm; 5 mm if HIV positive	19	NR	NR	36
Rusen et al. [27]	1999	Toronto, ON	167 IDUs	155	5 mm and 10 mm	31 (5 mm); 28 (10 mm)	0	Birth outside Canada, age ⩾35 years	5[a]
Salomon et al. [28]	2000	New York, NY	610 IDUs	566	10 mm; 5 mm if HIV positive or of unknown HIV status	15	9	History of TST positivity, age, duration of IDU[b]	21[a]
Askarian et al. [29]	2001	Shiraz, Iran	319 Drug users	…	10 mm	40	NR	Age, male sex, IDU	NR
Portilla et al. [30]	2001	Alicante, Spain	189 Drug users	NR	5 mm	59	NR	Older age	29
Howard et al. [31]	2002	Bronx, NY	806 Heroin users	793	10 mm; 5 mm if HIV positive	25	16	Separately reported for HIV-positive and HIV-negative subjects[c]	32
Portu et al. [32]	2002	Basque region, Spain	1131 IDUs	NR	5 mm	42	NR	HIV seronegativity	47
Quaglio et al. [33]	2002	Italy (city not specified)	252 Drug users	237	5 mm and 10 mm	26 (5 mm); 11 (10 mm)	NR	NR	21
Riley et al. [34]	2002	Baltimore, MD	286 IDUs	241	NR	17	NR	Longer smoking history, difficulty acquiring food, self-reported HIV infection	18[a]
Brassard et al. [35]	2004	Montreal, PQ	262 IDUs	246	5 mm	22	NR	Older age at first injection, duration of IDU, HIV negative	24
Grimes et al. [36]	2007	Houston, TX	123 Crack cocaine users	99	10 mm; 5 mm if HIV positive	28	NR	Crack cocaine use at home	7

NOTE. Only studies with ⩾50 subjects were included. BCG, bacille Calmette-Guérin; IDU, injection drug use; NR, not reported; TB, tuberculosis.

[a] Self-reported.

[b] Correlated; both were independently predictive in separate models.

[c] Among HIV-seronegative subjects, predictive factors included birth in Puerto Rico or foreign country, black ethnicity, self-reported TB exposure, employment as a home health aide, age ⩾35 years, and crack cocaine use. Among HIV-seropositive subjects, predictive factors included birth in Puerto Rico, self-reported TB exposure, alcoholism, and higher $CD4^+$ cell count.

Table 2. Summary of studies demonstrating elevated risk of tuberculosis (TB) among injection drug users (IDUs), compared with other HIV risk categories.

Study	Year	Study type	Study subjects	Country	Study date(s)	Selected findings
Markowitz et al. [11]	1993	Multicenter cross-sectional study	1171 HIV-positive patients	United States	1988–1990	IDUs more likely than MSM to have positive TST results (15% vs. 2.5%; $P < .001$)
Moreno et al. [76]	1993	Retrospective cohort study	706 HIV-positive patients	Spain	1985–1989	TB more frequent among IDUs with no previous isoniazid treatment (63 of 290; 22%) than among patients in other HIV-transmission categories (0 of 60; 0%)
Castilla et al. [77]	1995	National surveillance data analysis	22,445 Patients with AIDS	Spain	1988–1993	Highest proportions of extrapulmonary TB at AIDS diagnosis among HIV transmission categories (35%) observed for IDUs
Gollub et al. [78]	1997	Analysis of surveillance data of Philadelphia, PA	74 Cases of TB disease in AIDS registry	United States	1993	IDUs or individuals acquiring HIV through heterosexual sex are more likely to have TB disease than are MSM (OR, 3.3; 95% CI, 1.3–8.4)
Godoy et al. [79]	1998	National surveillance data analysis	2826 Patients with HIV and TB coinfection	Spain	1994	IDU is an independent predictor of TB among patients with AIDS (OR, 1.4; 95% CI, 1.2–1.6)
Jones et al. [80]	1998	Medical-records analysis from 9 US cities	15,588 MSM and 14,475 IDUs	United States	1991–1996	Higher incidence of TB cases among IDUs than among MSM
Morgello et al. [81]	2002	Retrospective analysis of autopsy data	394 HIV-infected adults	United States	1979–2000	TB associated with IDU but not with sexual risk
Calpe et al. [82]	2004	Analysis of surveillance data of Valencia, Spain	459 Patients with TB	Spain	1987–2001	59% of HIV-positive study patients had TB that was attributable to drug use
Girardi et al. [83]	2005	Multicenter prospective cohort study	22,217 HIV-positive patients	Multiple[a]	1996–2003	TB rate lower for MSM than for IDUs (RR, 2.46; 95% CI, 1.51–4.01)
Podlekareva et al. [84]	2006	EuroSIDA surveillance data	24,991 Patients with AIDS	Multiple[b]	1994–2005	IDU, not $CD4^+$ cell count, predicted risk of TB among patients with $CD4^+$ cell counts >300 cells/L (OR, 2.1; 95% CI, 1.1–4.2)
Muga et al. [85]	2007	Multicenter cohort study	2238 HIV seroconverters	Spain	1980–2004	IDUs more likely to develop TB (RH, 3.0; 95% CI, 1.72–5.26; $P < .001$)

NOTE. MSM, men who have sex with men; RH, relative hazard; RR, relative risk.

[a] Includes 13 European and North American cohort studies.

[b] Includes 28 European countries, Argentina, and Israel.

fused with TB prevention, a problem that itself has led to longer patient delay in some contexts [104].

Sociodemographic factors and attitudes also complicate the ability of drug users to initiate disease treatment. In a review of treatment utilization for hepatitis C virus among IDUs coinfected with HIV, Mehta et al. [105] identified several barriers to care, including low motivation for treatment (particularly when asymptomatic), unstable lifestyle, alcohol abuse, and lack of primary care or health insurance [105]. IDUs may also avoid seeking care because of a perceived stigma or fear that they may experience narcotic withdrawal if hospitalized [106]. At the provider level, the perception persists that drug users are a population that is difficult to treat [105–107], and low reimbursement rates for LTBI treatment have also been cited by physicians as a barrier [106].

Even when barriers to health care access are overcome, adherence to long treatment regimens can be particularly problematic for drug users. IDU [96, 108, 109], HIV seropositivity, [108], homelessness [8, 96, 110], and alcoholism [109, 110] have all been identified as risk factors for failure to complete TB treatment. Crack cocaine users in New York City had the highest rates of both regulatory intervention and detention for treatment completion, and regulatory action was associated with both crack cocaine and IDU [111]. Finally, in a study of 96 South African patients who failed to complete treatment for multidrug-resistant TB, illicit marijuana or sedative (mandrax) use during treatment was the most important factor [112]. The challenge of maintaining high levels of adherence has clear implications for TB control, which may require the provision and coordination of additional services for drug users, including targeted testing and treatment.

TARGETED TESTING FOR LTBI

The most common method of testing for LTBI remains tuberculin skin testing (TST), despite its many limitations [113]. TST induration of at least 15 mm is required for a positive test result, with general recommendations of cutoffs of 10 mm for IDUs and 5 mm for HIV-seropositive individuals [114], although the use of reduced cutoffs remains controversial [115–118]. Additional issues with TST include measurement reliability, the booster phenomenon (i.e., an initial TST provides an immunologic stimulus that can lead to subsequent false-positive test results), potential cross-reactivity among bacille Calmette-Guérin–vaccinated individuals, and anergic response in immunocompromised individuals. The Centers for Disease Control and Prevention no longer recommends testing for cutaneous anergy in HIV-infected persons [119], after 2 randomized controlled trials failed to demonstrate benefit of LTBI treatment for anergic individuals [120, 121]. After these trials, however, several observational studies demonstrated a reduced incidence of TB disease among anergic individuals who underwent treatment for LTBI [19, 76, 122].

The requirement for a return visit after TST has been particularly problematic for drug users and has resulted in creative attempts to facilitate targeted testing for LTBI. Compliance for a return read can be markedly improved with monetary incentives [21, 25, 123], whereas education and/or counseling are generally ineffective [21, 25]. Studies examining the validity of self-reported TST history and self-assessment of TST induration [124] have yielded mixed results [28, 125]. In Rotterdam, The Netherlands, establishment of a mobile unit providing chest radiographs for drug users and homeless persons contributed to a 50% decrease in TB incidence in this group [126]. In most contexts, however, TST remains the mainstay of targeted testing, although new methods demonstrate promise for improving case-finding among populations at high risk.

IFN-γ–release assays (IGRAs). An important recent development in TB diagnostics has been the introduction of IGRAs, in vitro tests based on the immune response to *Mycobacterium tuberculosis* antigens. Two diagnostic IGRAs are now commercially available—namely, QuantiFERON-TB Gold In-Tube (QFT-GIT; Cellestis) and T-SPOT-TB (Oxford Immunotec). The Centers for Disease Control and Prevention has recommended the use of an earlier IGRA, QuantiFERON-TB Gold, for all circumstances in which TST is currently used [127]. IGRA advantages include insensitivity to bacille Calmette-Guérin vaccination, lack of requirement of a return visit, and the absence of necessity of boosting, which is an important consideration for individuals who undergo repeated testing. QFT-GIT has also incorporated a positive control (mitogen) to account for a potential anergic response, yet the predictive value of IGRAs in immunocompromised persons remains uncertain. A full discussion of the IGRAs is beyond the scope of this article, and the reader is referred to other reviews for a better understanding of IGRA performance characteristics [113].

IGRAs have nonetheless been used in several studies involving drug users. A study of >1000 IDUs in the US-Mexican border city of Tijuana, Mexico, which is a region of TB endemicity, found 67% LTBI prevalence with use of QFT-GIT [128]. Elsewhere, a study of crack cocaine smokers in Houston, Texas, evaluated both QFT-GIT and T-SPOT-TB and found an LTBI prevalence of 34% with use of IGRAs and of 28% with use of TST [36]. Earlier studies comparing TST with a purified protein derivative-based IGRA (QuantiFERON) found much higher LTBI prevalence with use of the IGRAs (19%–65%), compared with use of TST (9%–30%) [16, 26]. These results again demonstrate the high prevalence of LTBI and may suggest increased sensitivity of IGRAs among drug users, although further research and validation of the tests are needed.

Table 3. Cost-benefit analyses for treatment of latent tuberculosis (TB) infection among drug users.

Study	Year	Context	No. of patients in model	Incentives incorporated into model	No. of patients completing treatment/eligible	Estimated no. of cases of TB prevented/years	Projected net cost savings, US dollars
Gourevitch et al. [141]	1998	MTP	507	No	151/184	11/5	285,284[a]
Snyder et al. [142]	1999	MTP	2689	Yes	285/378	30/10	104,660
Perlman et al. [143]	2001	SEP	1000[b]	Yes	175/175[b]	3/5	46,226

NOTE. MTP, methadone-treatment program; SEP, syringe exchange program.

[a] Assumes 65% isoniazid effectiveness (drug efficacy multiplied by adherence).

[b] Theoretical cohort of patients.

TREATMENT OF LTBI AND TB DISEASE

Cochrane database reviews have established the efficacy of LTBI treatment in reducing the incidence of TB disease among both HIV-seronegative individuals [129] and HIV-seropositive individuals [130]. Observational studies have shown decreased TB incidence among drug users after 6 months [131, 132] and 12 months [122] of isoniazid treatment. Currently, the Centers for Disease Control and Prevention recommends 9 months of once-daily treatment with isoniazid for HIV-negative individuals or an acceptable alternative of twice-weekly administration of isoniazid as directly observed therapy (DOT) [114].

A number of interventional studies have sought to identify methods for improving TB treatment adherence and completion among drug users. Drug treatment centers that use DOT have emerged as important sites for TB-related services [132–134], with studies demonstrating improved rates of treatment completion [133] and adherence [134] when DOT is provided on site. DOT has also improved drug users' adherence when used at drug treatment centers that combine LTBI treatment with monetary incentives [135–137] or methadone [138] and when used at other locations, including a public health department [139] or via street-based outreach [140]. DOT-based LTBI treatment for drug users has been shown to be cost-effective [141], even when monetary incentives are offered (table 3) [142, 143], which provides further justification for the integration of TB testing and treatment with other services for drug users [144–148].

Colocation of services can improve TB medication adherence and drug treatment outcomes [149]; however, sustaining these gains may depend on continued drug rehabilitation. For example, 73% of patients in 1 study failed to complete LTBI treatment because they were discharged from the drug treatment program that provided the medication [138]. Elsewhere, Casado et al. [150] conducted a follow-up study involving 131 HIV-seropositive individuals who had received 9 months of LTBI treatment. TB disease developed in 8 patients and was associated with continued drug abuse.

Fewer studies have reported on the treatment of TB disease among drug users, although high rates of treatment completion have been reported in several studies that included high proportions of drug-using patients [134, 151–156]. In a pilot study, DOT was combined with methadone administration at a prison infirmary and was linked to programs that provided treatment after release from prison; 9 of 10 recovering addicts were able to complete treatment [157]. As a result of favorable results from these demonstration studies and population-based modeling [158] and because it is thought to contribute to diminished drug resistance [159], DOT is generally advocated for treatment of TB among drug users. Nonetheless, a recent Cochrane database review found that DOT did not increase cure rates or rates of treatment completion [160]; this review, however, included only 2 studies conducted among IDUs, both of which used completion of LTBI treatment—and not resolution of TB disease—as an end point [137, 139].

SPECIAL TREATMENT CONSIDERATIONS

A number of unique considerations exist for treating TB in patients who use illicit drugs. Standard TB treatment regimens that include isoniazid, rifampin, and pyrazinamide can be hepatotoxic [161–163], which is an important consideration for IDUs, who have a high prevalence of chronic viral hepatitis [164, 165] and alcohol abuse [105]. In 1 study, patients with TB were at a 4–5-fold increased risk of developing drug-induced hepatitis if coinfected with viral hepatitis or HIV and were at a 14-fold increased risk if coinfected with both [166]. Drug-induced hepatitis associated with anti-TB medications has been studied in several different contexts [166–170]; although drug regimens and criteria for drug-induced hepatitis varied, the studies have uniformly established the safety of anti-TB drugs among individuals with viral hepatitis who undergo treatment for LTBI [167–169] and TB disease [166, 169, 170]. Among studies exploring predictive factors for drug-induced hepatitis [167, 168], current alcohol use conferred the most-consistent risk, again demonstrating the need to address substance abuse when treating TB among high-risk patients.

A second treatment consideration for drug users involves

rifampin, which is a potent inducer of hepatic microsomal enzymes that increases drug clearance and reduces the half-life of a wide range of drugs, including barbiturates and methadone [171, 172]. Incidentally, rifampin has also been reported to cause false-positive results of opiate immunoassays [173, 174]. Concurrent treatment with rifampin and methadone is safe, although the dose of methadone may need to be increased [172]; nonetheless, in patients taking both drugs, rifampin has been frequently discontinued because of nonserious adverse reactions [175]. A related drug, rifabutin, is a less potent inducer of hepatic enzymes [176] and was found, in 1 study, to have no effect on the pharmacokinetics of methadone, despite subjective symptoms of narcotic withdrawal [177]. Rifabutin is the preferred alternative for the treatment of TB disease among patients receiving HAART [178]. The effect of this drug on opiate immunoassays has not been studied, to our knowledge.

CONCLUSIONS

Drug users remain a group at high risk of TB infection and disease, and IDU has been an important factor in HIV-associated TB epidemics worldwide. Treatment barriers, including poor adherence and limited access to care, pose unique challenges for treatment of drug users but serve as modifiable risk factors that should be the focus of future interventions. Because treatment failure is the primary risk factor for the development of drug resistance [179], the importance of TB control among drug users is clear and requires the provision of additional services that are geared toward sustaining positive outcomes.

The successful treatment of LTBI and TB disease among drug users has been demonstrated in a variety of contexts. With close monitoring, special situations, including methadone maintenance or coinfection with viral hepatitis, can also be managed successfully. Available evidence abundantly demonstrates improved treatment adherence for drug users when DOT is provided, and this should remain an important strategy for TB control among drug users, particularly when it can be combined with drug rehabilitation. New approaches of targeted testing for LTBI hold promise for improved case finding, but further study, including the significance of anergic response and performance of IGRAs among immunosuppressed individuals, is warranted.

Increased attention to groups at high risk, such as drug users, is an important part of an overall strategy that has likely contributed to the decrease in TB prevalence that has been seen in many countries during the past decade. To sustain these gains and to help arrest TB epidemics worldwide, continued attention must be paid to populations at high risk, such as drug users and IDUs.

Acknowledgments

Financial support. National Institute of Drug Abuse (grant T32DA023356 to R.G.D. and T.C.R.), Hispanic Serving Health Professions Schools (support to R.G.D.), and US Agency for International Development (GSM-025 to R.S.G.).

Potential conflicts of interest. All authors: no conflicts.

References

1. Rhodes T, Ball A, Stimson GV, et al. HIV infection associated with drug injecting in the newly independent states, Eastern Europe: the social and economic context of epidemics. Addiction **1999**; 94: 1323–36.
2. Punnotok J, Shaffer N, Naiwatanakul T, et al. Human immunodeficiency virus–related tuberculosis and primary drug resistance in Bangkok, Thailand. Int J Tuberc Lung Dis **2000**; 4:537–43.
3. Van Rie A, Zhemkov V, Granskaya J, et al. TB and HIV in St. Petersburg, Russia: a looming catastrophe? Int J Tuberc Lung Dis **2005**;9: 740–5.
4. van der Werf MJ, Yegorova OB, Chentsova N, et al. Tuberculosis-HIV co-infection in Kiev City, Ukraine. Emerg Infect Dis **2006**; 12:766–8.
5. Mattos IG, Ribeiro MO, Netto IC, d'Azevedo PA. Tuberculosis: a study of 111 cases in an area of high prevalence in the extreme south of Brazil. Braz J Infect Dis **2006**; 10:194–8.
6. de Vries G, van Hest RA. From contact investigation to tuberculosis screening of drug addicts and homeless persons in Rotterdam. Eur J Public Health **2006**; 16:133–6.
7. Ngoc Buu T, Houben RM, Thi Quy H, Thi Ngoc Lan N, Borgdorff MW, Cobelens FG. HIV and tuberculosis in Ho Chi Minh City, Vietnam, 1997–2002. Emerg Infect Dis **2007**; 13:1463–9.
8. Story A, Murad S, Roberts W, Verheyen M, Hayward AC. Tuberculosis in London: the importance of homelessness, problem drug use and prison. Thorax **2007**; 62:667–71.
9. World Health Organization, Joint United Nations Programme on HIV/AIDS, and United Nations Office of Drugs and Crime. Policy guidelines for collaborative TB and HIV services for injecting and other drug users—an integrated approach. **2008**. Available at: http://whqlibdoc.who.int/publications/2008/9789241596930_eng.pdf. Accessed 8 September 2008.
10. Perlman DC, Salomon N, Perkins MP, Yancovitz S, Paone D, Des Jarlais DC. Tuberculosis in drug users. Clin Infect Dis **1995**; 21: 1253–64.
11. Markowitz N, Hansen NI, Wilcosky TC, et al. Tuberculin and anergy testing in HIV-seropositive and HIV-seronegative persons. Pulmonary Complications of HIV Infection Study Group. Ann Intern Med **1993**; 119:185–93.
12. Mathur ML, Chaudhary RC. Increased risk of tuberculosis in opium addicts. Indian J Med Sci **1996**; 50:365–7.
13. Friedman LN, Williams MT, Singh TP, Frieden TR. Tuberculosis, AIDS, and death among substance abusers on welfare in New York City. N Engl J Med **1996**; 334:828–33.
14. Keizer ST, Langendam MM, van Deutekom H, Coutinho RA, van Ameijden EJ. How does tuberculosis relate to HIV positive and HIV negative drug users? J Epidemiol Community Health **2000**; 54:64–8.
15. Reyes JC, Robles RR, Colon HM, Marrero CA, Castillo X, Melendez M. *Mycobacterium tuberculosis* infection among crack and injection drug users in San Juan, Puerto Rico. P R Health Sci J **1996**; 15:233–6.
16. Converse PJ, Jones SL, Astemborski J, Vlahov D, Graham NM. Comparison of a tuberculin interferon-γ assay with the tuberculin skin test in high-risk adults: effect of human immunodeficiency virus infection. J Infect Dis **1997**; 176:144–50.
17. Lifson AR, Grant SM, Lorvick J, et al. Two-step tuberculin skin testing of injection drug users recruited from community-based settings. Int J Tuberc Lung Dis **1997**; 1:128–34.
18. Strathdee SA, Patrick DM, Currie SL, et al. Needle exchange is not

enough: lessons from the Vancouver injecting drug use study. AIDS **1997**; 11:F59–65.
19. Daley CL, Hahn JA, Moss AR, Hopewell PC, Schecter GF. Incidence of tuberculosis in injection drug users in San Francisco: impact of anergy. Am J Respir Crit Care **1998**; 157:19–22.
20. Durante AJ, Selwyn PA, O'Connor PG. Risk factors for and knowledge of *Mycobacterium tuberculosis* infection among drug users in substance abuse treatment. Addiction **1998**; 93:1393–401.
21. Malotte CK, Rhodes F, Mais KE. Tuberculosis screening and compliance with return for skin test reading among active drug users. Am J Public Health **1998**; 88:792–6.
22. Robles RR, Marrero CA, Reyes JC, et al. Risk behaviors, HIV seropositivity, and tuberculosis infection in injecting drug users who operate shooting galleries in Puerto Rico. J Acquir Immune Defic Syndr Hum Retrovirol **1998**; 17:477–83.
23. Taubes T, Galanter M, Dermatis H, Westreich L. Crack cocaine and schizophrenia as risk factors for PPD reactivity in the dually diagnosed. J Addict Dis **1998**; 17:63–74.
24. Alvarez Rodriguez M, Godoy Garcia P. Prevalence of tuberculosis and HIV infections among participants in an intravenous drug user risk-control program [in Spanish]. Rev Esp Salud Publica **1999**; 73:375–81.
25. Malotte CK, Hollingshead JR, Rhodes F. Monetary versus nonmonetary incentives for TB skin test reading among drug users. Am J Prev Med **1999**; 16:182–8.
26. Kimura M, Converse PJ, Astemborski J, et al. Comparison between a whole blood interferon-γ release assay and tuberculin skin testing for the detection of tuberculosis infection among patients at risk for tuberculosis exposure. J Infect Dis **1999**; 179:1297–300.
27. Rusen ID, Yuan L, Millson ME. Prevalence of *Mycobacterium tuberculosis* infection among injection drug users in Toronto. CMAJ **1999**; 160:799–802.
28. Salomon N, Perlman DC, Friedmann P, Ziluck V, Des Jarlais DC. Prevalence and risk factors for positive tuberculin skin tests among active drug users at a syringe exchange program. Int J Tuberc Lung Dis **2000**; 4:47–54.
29. Askarian M, Karmi A, Sadeghi-Hassanabadi A. Tuberculosis among never-jailed drug abusers. East Mediterr Health J **2001**; 7:461–4.
30. Portilla J, Esteban J, Llinares R, et al. Prevalence of chronic hidden infections in a cohort of patients in substitutive treatment with methadone [in Spanish]. Med Clin (Barc) **2001**; 116:330–2.
31. Howard AA, Klein RS, Schoenbaum EE, Gourevitch MN. Crack cocaine use and other risk factors for tuberculin positivity in drug users. Clin Infect Dis **2002**; 35:1183–90.
32. Portu JJ, Aldamiz-Etxebarria M, Agud JM, Arevalo JM, Almaraz MJ, Ayensa C. Tuberculin skin testing in intravenous drug users: differences between HIV-seropositive and HIV-seronegative subjects. Addict Biol **2002**; 7:235–41.
33. Quaglio G, Lugoboni F, Talamini G, Lechi A, Mezzelani P. Prevalence of tuberculosis infection and comparison of multiple-puncture liquid tuberculin test and Mantoux test among drug users. Scand J Infect Dis **2002**; 34:574–6.
34. Riley ED, Vlahov D, Huettner S, Beilenson P, Bonds M, Chaisson RE. Characteristics of injection drug users who utilize tuberculosis services at sites of the Baltimore city needle exchange program. J Urban Health **2002**; 79:113–27.
35. Brassard P, Bruneau J, Schwartzman K, Senecal M, Menzies D. Yield of tuberculin screening among injection drug users. Int J Tuberc Lung Dis **2004**; 8:988–93.
36. Grimes CZ, Hwang LY, Williams ML, Austin CM, Graviss EA. Tuberculosis infection in drug users: interferon-gamma release assay performance. Int J Tuberc Lung Dis **2007**; 11:1183–9.
37. Friedman H, Newton C, Klein TW. Microbial infections, immunomodulation, and drugs of abuse. Clin Microbiol Rev **2003**; 16:209.
38. Wei G, Moss J, Yuan CS. Opioid-induced immunosuppression: is it centrally mediated or peripherally mediated? Biochem Pharmacol **2003**; 65:1761–6.
39. Kapadia F, Vlahov D, Donahoe RM, Friedland G. The role of substance abuse in HIV disease progression: reconciling differences from laboratory and epidemiologic investigations. Clin Infect Dis **2005**; 41: 1027–34.
40. Hudolin V. Tuberculosis and alcoholism. Ann N Y Acad Sci **1975**; 252:353–64.
41. Barclay DM 3rd, Richardson JP, Fredman L. Tuberculosis in the homeless. Arch Fam Med **1995**; 4:541–6.
42. Nelson S, Mason C, Bagby G, Summer W. Alcohol, tumor necrosis factor, and tuberculosis. Alcohol Clin Exp Res **1995**; 19:17–24.
43. Drobniewski FA, Balabanova YM, Ruddy MC, et al. Tuberculosis, HIV seroprevalence and intravenous drug abuse in prisoners. Eur Respir J **2005**; 26:298–304.
44. Altet-Gomez MN, Alcaide J, Godoy P, Romero MA, Hernandez del Rey I. Clinical and epidemiological aspects of smoking and tuberculosis: a study of 13,038 cases. Int J Tuberc Lung Dis **2005**; 9:430–6.
45. Niveau G. Prevention of infectious disease transmission in correctional settings: a review. Public Health **2006**; 120:33–41.
46. Hernandez-Garduno E, Cook V, Kunimoto D, Elwood RK, Black WA, FitzGerald JM. Transmission of tuberculosis from smear negative patients: a molecular epidemiology study. Thorax **2004**; 59:286–90.
47. Wang W, Xiao H, Lu L. Case-control retrospective study of pulmonary tuberculosis in heroin-abusing patients in China. J Psychoactive Drugs **2006**; 38:203–5.
48. Epstein MD, Schluger NW, Davidow AL, Bonk S, Rom WN, Hanna B. Time to detection of *Mycobacterium tuberculosis* in sputum culture correlates with outcome in patients receiving treatment for pulmonary tuberculosis. Chest **1998**; 113:379–86.
49. Alpert PL, Munsiff SS, Gourevitch MN, Greenberg B, Klein RS. A prospective study of tuberculosis and human immunodeficiency virus infection: clinical manifestations and factors associated with survival. Clin Infect Dis **1997**; 24:661–8.
50. Kourbatova EV, Borodulin BE, Borodulina EA, del Rio C, Blumberg HM, Leonard MK Jr. Risk factors for mortality among adult patients with newly diagnosed tuberculosis in Samara, Russia. Int J Tuberc Lung Dis **2006**; 10:1224–30.
51. Cayla JA, Garcia de Olalla P, Galdos-Tanguis H, et al. The influence of intravenous drug use and HIV infection in the transmission of tuberculosis. AIDS **1996**; 10:95–100.
52. Rodrigo T, Cayla JA, Garcia de Olalla P, et al. Characteristics of tuberculosis patients who generate secondary cases. Int J Tuberc Lung Dis **1997**; 1:352–7.
53. Friedman CR, Quinn GC, Kreiswirth BN, et al. Widespread dissemination of a drug-susceptible strain of *Mycobacterium tuberculosis.* J Infect Dis **1997**; 176:478–84.
54. Chin DP, DeRiemer K, Small PM, et al. Differences in contributing factors to tuberculosis incidence in US-born and foreign-born persons. Am J Respir Crit Care Med **1998**; 158:1797–803.
55. Iñigo Martínez J, Chaves Sánchez F, Arce Arnáez A, et al. Recent transmission of tuberculosis in Madrid (Spain): usefulness of molecular techniques [in Spanish]. Med Clin (Barc) **2000**; 115:241–5.
56. Fernandez de la Hoz K, Inigo J, Fernandez-Martin JI, et al. The influence of HIV infection and imprisonment on dissemination of *Mycobacterium tuberculosis* in a large Spanish city. Int J Tuberc Lung Dis **2001**; 5:696–702.
57. Hernandez-Garduno E, Kunimoto D, Wang L, et al. Predictors of clustering of tuberculosis in greater Vancouver: a molecular epidemiologic study. CMAJ **2002**; 167:349–52.
58. FitzGerald JM, Fanning A, Hoepnner V, Hershfield E, Kunimoto D. The molecular epidemiology of tuberculosis in western Canada. Int J Tuberc Lung Dis **2003**; 7:132–8.
59. Driver CR, Kreiswirth B, Macaraig M, et al. Molecular epidemiology of tuberculosis after declining incidence, New York City, 2001–2003. Epidemiol Infect **2007**; 135:634–43.
60. Alland D, Kalkut GE, Moss AR, et al. Transmission of tuberculosis

in New York City: an analysis by DNA fingerprinting and conventional epidemiologic methods. N Engl J Med **1994**; 330:1710–6.
61. Palmero D, Ritacco V, Ambroggi M, et al. Multidrug-resistant tuberculosis in AIDS patients at the beginning of the millennium [in Spanish]. Medicina (B Aires) **2006**; 66:399–404 (erratum: Medicina (B Aires) 2006; 66:598).
62. Morozova I, Riekstina V, Sture G, Wells C, Leimane V. Impact of the growing HIV-1 epidemic on multidrug-resistant tuberculosis control in Latvia. Int J Tuberc Lung Dis **2003**; 7:903–6.
63. Hannan MM, Peres H, Maltez F, et al. Investigation and control of a large outbreak of multi-drug resistant tuberculosis at a central Lisbon hospital. J Hosp Infect **2001**; 47:91–7.
64. Conover C, Ridzon R, Valway S, et al. Outbreak of multidrug-resistant tuberculosis at a methadone treatment program. Int J Tuberc Lung Dis **2001**; 5:59–64.
65. Kenyon TA, Ridzon R, Luskin-Hawk R, et al. A nosocomial outbreak of multidrug-resistant tuberculosis. Ann Intern Med **1997**; 127:32–6.
66. Centers for Disease Control and Prevention. Crack cocaine use among persons with tuberculosis—Contra Costa County, California, 1987–1990. MMWR Morb Mortal Wkly Rep **1991**; 40:485–9.
67. Leonhardt KK, Gentile F, Gilbert BP, Aiken M. A cluster of tuberculosis among crack house contacts in San Mateo County, California. Am J Public Health **1994**; 84:1834–6.
68. Sterling TR, Thompson D, Stanley RL, et al. A multi-state outbreak of tuberculosis among members of a highly mobile social network: implications for tuberculosis elimination. Int J Tuberc Lung Dis **2000**; 4:1066–73.
69. Munckhof WJ, Konstantinos A, Wamsley M, Mortlock M, Gilpin C. A cluster of tuberculosis associated with use of a marijuana water pipe. Int J Tuberc Lung Dis **2003**; 7:860–5.
70. Oeltmann JE, Oren E, Haddad MB, et al. Tuberculosis outbreak in marijuana users, Seattle, Washington, 2004. Emerg Infect Dis **2006**; 12:1156–9.
71. Perlman DC, Perkins MP, Paone D, et al. "Shotgunning" as an illicit drug smoking practice. J Subst Abuse Treat **1997**; 14:3–9.
72. Riley ED, Chaisson RE, Robnett TJ, Vertefeuille J, Strathdee SA, Vlahov D. Use of audio computer-assisted self-interviews to assess tuberculosis-related risk behaviors. Am J Respir Crit Care Med **2001**; 164:82–5.
73. McElroy RD, Rothenberg RB, Varghese R, et al. A network-informed approach to investigating a tuberculosis outbreak: implications for enhancing contact investigations. Int J Tuberc Lung Dis **2003**; 7: S486–93.
74. Reichman LB, Felton CP, Edsall JR. Drug dependence, a possible new risk factor for tuberculosis disease. Arch Intern Med **1979**; 139:337–9.
75. Selwyn PA, Hartel D, Lewis VA, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N Engl J Med **1989**; 320:545–50.
76. Moreno S, Baraia-Etxaburu J, Bouza E, et al. Risk for developing tuberculosis among anergic patients infected with HIV. Ann Intern Med **1993**; 119:194–8.
77. Castilla J, Gutierrez-Rodriguez A, Tello O. Sociodemographic predictors and temporal trends of extrapulmonary tuberculosis as an AIDS-defining disease in Spain. AIDS **1995**; 9:383–8.
78. Gollub EL, Trino R, Salmon M, Moore L, Dean JL, Davidson BL. Co-occurrence of AIDS and tuberculosis: results of a database "match" and investigation. J Acquir Immune Defic Syndr Hum Retrovirol **1997**; 16:44–9.
79. Godoy P, Castilla J, Rullan JV. Incidence and risk factors of the association of AIDS and tuberculosis in Spain [in Spanish]. Med Clin (Barc) **1998**; 110:205–8.
80. Jones JL, Hanson DL, Dworkin MS, Kaplan JE, Ward JW. Trends in AIDS-related opportunistic infections among men who have sex with men and among injecting drug users, 1991–1996. J Infect Dis **1998**; 178:114–20.
81. Morgello S, Mahboob R, Yakoushina T, Khan S, Hague K. Autopsy findings in a human immunodeficiency virus-infected population over 2 decades: influences of gender, ethnicity, risk factors, and time. Arch Pathol Lab Med **2002**; 126:182–90.
82. Calpe JL, Chiner E, Marin-Pardo J, Calpe A, Armero V. Impact of the human immunodeficiency virus on the epidemiology of tuberculosis in area 15 of the Valencian community in Spain. Int J Tuberc Lung Dis **2004**; 8:1204–12.
83. Girardi E, Sabin CA, d'Arminio Monforte A, et al. Incidence of tuberculosis among HIV-infected patients receiving highly active antiretroviral therapy in Europe and North America. Clin Infect Dis **2005**; 41:1772–82.
84. Podlekareva D, Mocroft A, Dragsted UB, et al. Factors associated with the development of opportunistic infections in HIV-1–infected adults with high $CD4^+$ cell counts: a EuroSIDA study. J Infect Dis **2006**; 194:633–41.
85. Muga R, Ferreros I, Langohr K, et al. Changes in the incidence of tuberculosis in a cohort of HIV-seroconverters before and after the introduction of HAART. AIDS **2007**; 21:2521–7.
86. Rubinstien EM, Madden GM, Lyons RW. Active tuberculosis in HIV-infected injecting drug users from a low-rate tuberculosis area. J Acquir Immune Defic Syndr Hum Retrovirol **1996**; 11:448–54.
87. Markowitz N, Hansen NI, Hopewell PC, et al. Incidence of tuberculosis in the United States among HIV-infected persons. Pulmonary Complications of HIV Infection Study Group. Ann Intern Med **1997**; 126:123–32.
88. van Asten L, Langendam M, Zangerle R, et al. Tuberculosis risk varies with the duration of HIV infection: a prospective study of European drug users with known date of HIV seroconversion. AIDS **2003**; 17: 1201–8.
89. Perez-Perdomo R, Perez-Cardona CM. An epidemiological review of tuberculosis in the Puerto Rican population. P R Health Sci J **1999**; 18: 117–22.
90. Sanchez-Carbonell X, Vilaregut A. A 10-year follow-up study on the health status of heroin addicts based on official registers. Addiction **2001**; 96:1777–86.
91. Pérez-Agudo F, Alonso Moreno FJ, Urbina Torija J. Prevalence of human immunodeficiency virus type 1 and *Mycobacterium tuberculosis* infections in a prison population in the years 1989 to 1995 [in Spanish]. Med Clin (Barc) **1998**; 110:167–70.
92. Martin V, Cayla JA, Bolea A, Castilla J. *Mycobacterium tuberculosis* and human immunodeficiency virus co-infection in intravenous drug users on admission to prison. Int J Tuberc Lung Dis **2000**; 4:41–6.
93. Agarwal AK, Singh NY, Devi LB, Shyamkanhai KH, Singh YM, Bhattacharya SK. Clinical features & HIV progression as observed longitudinally in a cohort of injecting drug users in Manipur. Indian J Med Res **1998**; 108:51–7.
94. Sungkanuparph S, Vibhagool A, Mootsikapun P, Chetchotisakd P, Tansuphaswaswadikul S, Bowonwatanuwong C. Opportunistic infections after the initiation of highly active antiretroviral therapy in advanced AIDS patients in an area with a high prevalence of tuberculosis. AIDS **2003**; 17:2129–31.
95. Pilote L, Tulsky JP, Zolopa AR, Hahn JA, Schecter GF, Moss AR. *Tuberculosis prophylaxis* in the homeless: a trial to improve adherence to referral. Arch Intern Med **1996**; 156:161–5.
96. Pablos-Méndez A, Knirsch CA, Barr RG, Lerner BH, Frieden TR. Nonadherence in tuberculosis treatment: predictors and consequences in New York City. Am J Med **1997**; 102:164–70.
97. Diez M, Bleda MJ, Alcaide J, et al. Determinants of patient delay among tuberculosis cases in Spain. Eur J Public Health **2004**; 14:151–5.
98. Golub JE, Bur S, Cronin WA, et al. Delayed tuberculosis diagnosis and tuberculosis transmission. Int J Tuberc Lung Dis **2006**; 10:24–30.
99. Hanna DB, Gupta LS, Jones LE, Thompson DM, Kellerman SE, Sackoff JE. AIDS-defining opportunistic illnesses in the HAART era in New York City. AIDS Care **2007**; 19:264–72.
100. Morice AH, Menon MS, Mulrennan SA, et al. Opiate therapy in chronic cough. Am J Respir Crit Care Med **2007**; 175:312–5.

101. Salomon N, Perlman DC, Friedmann P, et al. Knowledge of tuberculosis among drug users: relationship to return rates for tuberculosis screening at a syringe exchange. J Subst Abuse Treat **1999**; 16:229–35.
102. Nyamathi A, Sands H, Pattatucci-Aragon A, Berg J, Leake B. Tuberculosis knowledge, perceived risk and risk behaviors among homeless adults: effect of ethnicity and injection drug use. J Community Health **2004**; 29:483–97.
103. Wolfe H, Marmor M, Maslansky R, et al. Tuberculosis knowledge among New York City injection drug users. Am J Public Health **1995**; 85:985–8.
104. Ngamvithayapong J, Winkvist A, Diwan V. High AIDS awareness may cause tuberculosis patient delay: results from an HIV epidemic area, Thailand. AIDS **2000**; 14:1413–9.
105. Mehta SH, Thomas DL, Sulkowski MS, Safaein M, Vlahov D, Strathdee SA. A framework for understanding factors that affect access and utilization of treatment for hepatitis C virus infection among HCV–mono-infected and HIV/HCV–co-infected injection drug users. AIDS **2005**; 19(Suppl 3):S179–89.
106. Curtis R, Friedman SR, Neaigus A, Jose B, Goldstein M, Des Jarlais DC. Implications of directly observed therapy in tuberculosis control measures among IDUs. Public Health Rep **1994**; 109:319–27.
107. Edlin BR, Kresina TF, Raymond DB, et al. Overcoming barriers to prevention, care, and treatment of hepatitis C in illicit drug users. Clin Infect Dis **2005**; 40(Suppl 5):S276–85.
108. Wobeser W, Yuan L, Naus M. Outcome of pulmonary tuberculosis treatment in the tertiary care setting—Toronto 1992/93. Tuberculosis Treatment Completion Study Group. CMAJ **1999**; 160:789–94.
109. Gelmanova IY, Keshavjee S, Golubchikova VT, et al. Barriers to successful tuberculosis treatment in Tomsk, Russian Federation: nonadherence, default and the acquisition of multidrug resistance. Bull World Health Organ **2007**; 85:703–11.
110. Burman WJ, Cohn DL, Rietmeijer CA, Judson FN, Sbarbaro JA, Reves RR. Noncompliance with directly observed therapy for tuberculosis: epidemiology and effect on the outcome of treatment. Chest **1997**; 111:1168–73.
111. Gasner MR, Maw KL, Feldman GE, Fujiwara PI, Frieden TR. The use of legal action in New York City to ensure treatment of tuberculosis. N Engl J Med **1999**; 340:359–66.
112. Holtz TH, Lancaster J, Laserson KF, Wells CD, Thorpe L, Weyer K. Risk factors associated with default from multidrug-resistant tuberculosis treatment, South Africa, 1999–2001. Int J Tuberc Lung Dis **2006**; 10:649–55.
113. Menzies D, Pai M, Comstock G. Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research. Ann Intern Med **2007**; 146:340–54.
114. American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR Recomm Rep **2000**; 49(RR-6):1–51.
115. Graham NM, Nelson KE, Solomon L, et al. Prevalence of tuberculin positivity and skin test anergy in HIV-1–seropositive and –seronegative intravenous drug users. JAMA **1992**; 267:369–73.
116. Gourevitch MN, Hartel D, Schoenbaum EE, Klein RS. Lack of association of induration size with HIV infection among drug users reacting to tuberculin. Am J Respir Crit Care Med **1996**; 154:1029–33.
117. Klein RS, Gourevitch MN, Teeter R, Schoenbaum EE. The incidence of tuberculosis in drug users with small tuberculin reaction sizes. Int J Tuberc Lung Dis **2001**; 5:707–11.
118. Cobelens FG, Egwaga SM, van Ginkel T, Muwinge H, Matee MI, Borgdorff MW. Tuberculin skin testing in patients with HIV infection: limited benefit of reduced cutoff values. Clin Infect Dis **2006**; 43: 634–9.
119. Centers for Disease Control and Prevention. Anergy skin testing and tuberculosis [corrected] preventive therapy for HIV-infected persons: revised recommendations. MMWR Recomm Rep **1997**; 46(RR-15): 1–10.
120. Gordin FM, Matts JP, Miller C, et al. A controlled trial of isoniazid in persons with anergy and human immunodeficiency virus infection who are at high risk for tuberculosis. Terry Beirn Community Programs for Clinical Research on AIDS. N Engl J Med **1997**; 337:315–20.
121. Whalen CC, Johnson JL, Okwera A, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. Uganda–Case Western Reserve University Research Collaboration. N Engl J Med **1997**; 337:801–8.
122. Gourevitch MN, Hartel D, Selwyn PA, Schoenbaum EE, Klein RS. Effectiveness of isoniazid chemoprophylaxis for HIV-infected drug users at high risk for active tuberculosis. AIDS **1999**; 13:2069–74.
123. FitzGerald JM, Patrick DM, Strathdee S, et al. Use of incentives to increase compliance for TB screening in a population of intravenous drug users. Vancouver Injection Drug Use Study Group. Int J Tuberc Lung Dis **1999**; 3:153–5.
124. Gourevitch MN, Teeter R, Schoenbaum EE, Klein RS. Self-assessment of tuberculin skin test reactions by drug users with or at risk for human immunodeficiency virus infection. Int J Tuberc Lung Dis **1999**; 3:321–5.
125. Kunins HV, Howard AA, Klein RS, et al. Validity of a self-reported history of a positive tuberculin skin test: a prospective study of drug users. J Gen Intern Med **2004**; 19:1039–44.
126. de Vries G, van Hest RA, Richardus JH. Impact of mobile radiographic screening on tuberculosis among drug users and homeless persons. Am J Respir Crit Care Med **2007**; 176:201–7.
127. Mazurek GH, Jereb J, Lobue P, Iademarco MF, Metchock B, Vernon A. Guidelines for using the QuantiFERON-TB Gold test for detecting *Mycobacterium tuberculosis* infection, United States. MMWR Recomm Rep **2005**; 54(RR-15):49–55.
128. Garfein RS, Rodwell T, Brouwer KC, et al. Use of QuantiFERON-TB Gold In Tube assay to estimate the prevalence of *M. tuberculosis* infection among injection drug users at risk for HIV in Tijuana, Mexico. In: Proceedings and abstracts of the 1st Global Symposium on Interferon-γ Assays (Vancouver, Canada). Victoria, Australia: Cellestis, **2007**.
129. Smieja MJ, Marchetti CA, Cook DJ, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. Cochrane Database Syst Rev **2000**; CD001363.
130. Woldehanna S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database Syst Rev **2004**; CD000171.
131. Graham NM, Galai N, Nelson KE, et al. Effect of isoniazid chemoprophylaxis on HIV-related mycobacterial disease. Arch Intern Med **1996**; 156:889–94.
132. Scholten JN, Driver CR, Munsiff SS, et al. Effectiveness of isoniazid treatment for latent tuberculosis infection among human immunodeficiency virus (HIV)–infected and HIV-uninfected injection drug users in methadone programs. Clin Infect Dis **2003**; 37:1686–92.
133. Batki SL, Gruber VA, Bradley JM, Bradley M, Delucchi K. A controlled trial of methadone treatment combined with directly observed isoniazid for tuberculosis prevention in injection drug users. Drug Alcohol Depend **2002**; 66:283–93.
134. Gourevitch MN, Wasserman W, Panero MS, Selwyn PA. Successful adherence to observed prophylaxis and treatment of tuberculosis among drug users in a methadone program. J Addict Dis **1996**; 15: 93–104.
135. Lorvick J, Thompson S, Edlin BR, Kral AH, Lifson AR, Watters JK. Incentives and accessibility: a pilot study to promote adherence to TB prophylaxis in a high-risk community. J Urban Health **1999**; 76: 461–7.
136. Tulsky JP, Pilote L, Hahn JA, et al. Adherence to isoniazid prophylaxis in the homeless: a randomized controlled trial. Arch Intern Med **2000**; 160:697–702.
137. Malotte CK, Hollingshead JR, Larro M. Incentives vs. outreach workers for latent tuberculosis treatment in drug users. Am J Prev Med **2001**; 20:103–7.
138. O'Connor PG, Shi JM, Henry S, Durante AJ, Friedman L, Selwyn

PA. Tuberculosis chemoprophylaxis using a liquid isoniazid-methadone admixture for drug users in methadone maintenance. Addiction **1999**; 94:1071–5.
139. Chaisson RE, Barnes GL, Hackman J, et al. A randomized, controlled trial of interventions to improve adherence to isoniazid therapy to prevent tuberculosis in injection drug users. Am J Med **2001**; 110: 610–5.
140. Nyamathi A, Nahid P, Berg J, et al. Efficacy of nurse case-managed intervention for latent tuberculosis among homeless subsamples. Nurs Res **2008**; 57:33–9.
141. Gourevitch MN, Alcabes P, Wasserman WC, Arno PS. Cost-effectiveness of directly observed chemoprophylaxis of tuberculosis among drug users at high risk for tuberculosis. Int J Tuberc Lung Dis **1998**;2: 531–40.
142. Snyder DC, Paz EA, Mohle-Boetani JC, Fallstad R, Black RL, Chin DP. Tuberculosis prevention in methadone maintenance clinics: effectiveness and cost-effectiveness. Am J Respir Crit Care Med **1999**; 160:178–85.
143. Perlman DC, Gourevitch MN, Trinh C, Salomon N, Horn L, Des Jarlais DC. Cost-effectiveness of tuberculosis screening and observed preventive therapy for active drug injectors at a syringe-exchange program. J Urban Health **2001**; 78:550–67.
144. Altarac D, Dansky SF. Tuberculosis treatment through directly observed therapy in a large multisite methadone maintenance treatment program: addressing the public health needs of a high-risk population. J Public Health Manag Pract **1995**; 1:40–7.
145. Foley ME, Ehr AP, Raza B, Devlin CJ. Tuberculosis surveillance in a therapeutic community. J Addict Dis **1995**; 14:55–65.
146. Friedmann PD, D'Aunno TA, Jin L, Alexander JA. Medical and psychosocial services in drug abuse treatment: do stronger linkages promote client utilization? Health Serv Res **2000**; 35:443–65.
147. Greenberg AE, Tappero J, Choopanya K, et al. CDC international HIV prevention research activities among injection drug users in Thailand and Russia. J Urban Health **2005**; 82(3 Suppl 4):24–33.
148. Sylla L, Bruce RD, Kamarulzaman A, Altice FL. Integration and colocation of HIV/AIDS, tuberculosis and drug treatment services. Int J Drug Policy **2007**; 18:306–12.
149. Elk R, Schmitz J, Spiga R, Rhoades H, Andres R, Grabowski J. Behavioral treatment of cocaine-dependent pregnant women and TB-exposed patients. Addict Behav **1995**; 20:533–42.
150. Casado JL, Moreno S, Fortun J, et al. Risk factors for development of tuberculosis after isoniazid chemoprophylaxis in human immunodeficiency virus–infected patients. Clin Infect Dis **2002**; 34:386–9.
151. McDonald RJ, Memon AM, Reichman LB. Successful supervised ambulatory management of tuberculosis treatment failures. Ann Intern Med **1982**; 96:297–302.
152. Schluger N, Ciotoli C, Cohen D, Johnson H, Rom WN. Comprehensive tuberculosis control for patients at high risk for noncompliance. Am J Respir Crit Care Med **1995**; 151:1486–90.
153. el-Sadr W, Medard F, Berthaud V. Directly observed therapy for tuberculosis: the Harlem Hospital experience, 1993. Am J Public Health **1996**; 86:1146–9.
154. Caminero JA, Pavon JM, Rodriguez de Castro F, et al. Evaluation of a directly observed six months fully intermittent treatment regimen for tuberculosis in patients suspected of poor compliance. Thorax **1996**; 51:1130–3.
155. Salomon N, Perlman DC, Rubenstein A, Mandelman D, McKinley FW, Yancovitz SR. Implementation of universal directly observed therapy at a New York City hospital and evaluation of an out-patient directly observed therapy program. Int J Tuberc Lung Dis **1997**; 1: 397–404.
156. Smirnoff M, Goldberg R, Indyk L, Adler JJ. Directly observed therapy in an inner city hospital. Int J Tuberc Lung Dis **1998**; 2:134–9.
157. Marco A, Cayla JA, Serra M, et al. Predictors of adherence to tuberculosis treatment in a supervised therapy programme for prisoners before and after release. Study Group of Adherence to Tuberculosis Treatment of Prisoners. Eur Respir J **1998**; 12:967–71.
158. Chaulk CP, Friedman M, Dunning R. Modeling the epidemiology and economics of directly observed therapy in Baltimore. Int J Tuberc Lung Dis **2000**; 4:201–7.
159. Rusen ID, Ait-Khaled N, Alarcon E, et al. Cochrane systematic review of directly observed therapy for treating tuberculosis: good analysis of the wrong outcome. Int J Tuberc Lung Dis **2007**; 11:120–1.
160. Volmink J, Garner P. Directly observed therapy for treating tuberculosis. Cochrane Database Syst Rev **2006**; CD003343.
161. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin: a meta-analysis. Chest **1991**; 99:465–71.
162. Mitchell I, Wendon J, Fitt S, Williams R. Anti-tuberculous therapy and acute liver failure. Lancet **1995**; 345:555–6.
163. Ijaz K, Jereb JA, Lambert LA, et al. Severe or fatal liver injury in 50 patients in the United States taking rifampin and pyrazinamide for latent tuberculosis infection. Clin Infect Dis **2006**; 42:346–55.
164. Lemberg BD, Shaw-Stiffel TA. Hepatic disease in injection drug users. Infect Dis Clin North Am **2002**; 16:667–79.
165. Kuniholm MH, Mark J, Aladashvili M, et al. Risk factors and algorithms to identify hepatitis C, hepatitis B, and HIV among Georgian tuberculosis patients. Int J Infect Dis **2008**; 12:51–6.
166. Ungo JR, Jones D, Ashkin D, et al. Antituberculosis drug-induced hepatotoxicity: the role of hepatitis C virus and the human immunodeficiency virus. Am J Respir Crit Care Med **1998**; 157:1871–6.
167. Sadaphal P, Astemborski J, Graham NM, et al. Isoniazid preventive therapy, hepatitis C virus infection, and hepatotoxicity among injection drug users infected with *Mycobacterium tuberculosis.* Clin Infect Dis **2001**; 33:1687–91.
168. Fernandez-Villar A, Sopena B, Vazquez R, et al. Isoniazid hepatotoxicity among drug users: the role of hepatitis C. Clin Infect Dis **2003**;36: 293–8.
169. Padmapriyadarsini C, Chandrabose J, Victor L, Hanna LE, Arunkumar N, Swaminathan S. Hepatitis B or hepatitis C co-infection in individuals infected with human immunodeficiency virus and effect of anti-tuberculosis drugs on liver function. J Postgrad Med **2006**; 52:92–6.
170. Kwon YS, Koh WJ, Suh GY, Chung MP, Kim H, Kwon OJ. Hepatitis C virus infection and hepatotoxicity during antituberculosis chemotherapy. Chest **2007**; 131:803–8.
171. Kreek MJ, Garfield JW, Gutjahr CL, Giusti LM. Rifampin-induced methadone withdrawal. N Engl J Med **1976**; 294:1104–6.
172. Raistrick D, Hay A, Wolff K. Methadone maintenance and tuberculosis treatment. BMJ **1996**; 313:925–6.
173. de Paula M, Saiz LC, Gonzalez-Revalderia J, Pascual T, Alberola C, Miravalles E. Rifampicin causes false-positive immunoassay results for urine opiates. Clin Chem Lab Med **1998**; 36:241–3.
174. Daher R, Haidar JH, Al-Amin H. Rifampin interference with opiate immunoassays. Clin Chem **2002**; 48:203–4.
175. Cook SV, Fujiwara PI, Frieden TR. Rates and risk factors for discontinuation of rifampicin. Int J Tuberc Lung Dis **2000**; 4:118–22.
176. Blaschke TF, Skinner MH. The clinical pharmacokinetics of rifabutin. Clin Infect Dis **1996**; 22(Suppl 1):S15–21.
177. Brown LS, Sawyer RC, Li R, Cobb MN, Colborn DC, Narang PK. Lack of a pharmacologic interaction between rifabutin and methadone in HIV-infected former injecting drug users. Drug Alcohol Depend **1996**; 43:71–7.
178. Centers for Disease Control and Prevention. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: principles of therapy and revised recommendations. MMWR Recomm Rep **1998**; 47(RR-20):1–58.
179. Sharma SK, Mohan A. Multidrug-resistant tuberculosis: a menace that threatens to destabilize tuberculosis control. Chest **2006**; 130:261–72.