Published in final edited form as:
Clin Infect Dis. 2009 January 1; 48(1): . doi:10.1086/594126.

Tuberculosis and Drug Use: Review and Update

Robert G. Deiss[1], **Timothy C. Rodwell**[1], and **Richard S. Garfein**[1]
[1]University of California, San Diego. Department of Family and Preventive Medicine, Division of International Health and Cross-Cultural Medicine. La Jolla, California

Abstract

Illicit drug users continue to be a group at high risk for tuberculosis (TB) infection and disease. In this article, we present an updated review on the relationship between TB and drug use, summarizing 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 drug users remains an important component of a comprehensive TB strategy, but drug users present a unique set of challenges for TB diagnosis and control. New diagnostic modalities, including interferon-γ release assays (IGRAs), offer potential for improved diagnosis and surveillance among this group, alongside proven treatment strategies which incorporate the use of directly-observed therapy (DOT) with treatment for drug abuse. Special considerations, including co-infection with viral hepatitis and the Rifampin/methadone drug interaction, warrant clinical attention and are also updated here.

Keywords

Tuberculosis; injection drug use; drug use; epidemiology

Introduction

Drug use and injection drug use are important factors in the epidemiology of tuberculosis (TB) in developed and developing countries[1–8]. While the incidence of TB in most industrialized nations has declined over the past decade, the burden of disease is being increasingly borne by urban sub-populations, including drug users. Recognizing the important relationship between TB and drug use, the World Health Organization (WHO), UNAIDS and the UN Office on Drugs and Crime (UNODC) recently issued a set of guidelines to better coordinate TB care among drug users[9]. A comprehensive literature review, however, has not been published since 1995[10], while a number of studies have since proposed new approaches to the diagnosis and treatment of TB in this high-risk group. 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 including tuberculosis, 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 these articles and included additional manuscripts that were of historical

Corresponding Author: Robert Deiss Division of International Health University of California, San Diego 9500 Gilman Drive MC 0622 La Jolla, CA 92093-0622 rgdeiss@gmail.com. **Alternate correspondence:** Richard S. Garfein Division of International Health University of California, San Diego 9500 Gilman Drive MC 0622 La Jolla, CA 92093-0622 tel: (858) 822-3018 fax: (858) 534-4642 rgarfein@ucsd.edu.

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 term "injection drug users (IDUs)" refers only to studies which specified IDUs as their study population. The term "drug users" is used when referring to a study or group of studies with a heterogeneous population of drug users that may or may not include injection drug users. Overlap between these groups is not expected to be methodologically important, as studies comparing TB among IDUs with non-injection drug users have not found consistent and important differences with respect to TB (see below).

TB Risk and Prevalence among Drug Users

Drug use has been associated with higher prevalence of latent TB infection (LTBI)[11, 12], and incidence of 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 are most commonly associated with LTBI. Studies comparing the LTBI prevalence of IDUs with non-injection drug users have yielded mixed results [15, 20, 21, 23, 25, 29, 31], indicating that these groups share similar risk for 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]. While the clinical implications of this evidence remains unclear[39], drug use is frequently associated with a number of epidemiologic factors, including tobacco use, homelessness, alcohol abuse and incarceration, which confer additional risk for TB[40–45]. Together, these physiological and epidemiological factors may each contribute to observed outcomes, that drug users are more likely to be infectious[8, 46, 47], take longer to achieve negative culture[47, 48], and be at increased risk for 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 epidemiologic studies[6, 53–59] demonstrates that a disproportionate incidence of TB disease among drug users results from TB transmission, with the presence of identical DNA patterns ("clusters") between TB isolates implying recent transmission[60]. Cluster analysis has been used to identify outbreaks of drug-resistant TB among drug users in England[8] and multi-drug resistant TB (MDR-TB) in Thailand[2], Argentina[61], Latvia[62] and Portugal[63]. In the U.S., a TB outbreak occurred at a methadone treatment program [64], with one patient subsequently becoming the source case for a hospital outbreak of MDR-TB[65]. TB outbreaks among non-injecting drug users have also been attributed to sharing drug equipment or cramped conditions and poor ventilation [66–70]. "Shotgunning," a practice of inhaling then exhaling smoke 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].

Though 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 (see Table 2) demonstrates that IDUs are at greater risk for TB infection[11] and disease[76–85] relative to other HIV-associated risk groups, though this is sometimes confounded by regional or ethnic factors[77, 86–88]. High prevalence of TB co-infection is commonly reported among HIV-positive IDUs[89, 90], particularly in prison[43, 91, 92]. TB is often the most common opportunistic infection (OI) in endemic areas[77, 93, 94], and it is also seen among IDUs even in low prevalence

areas[86]. Risk for TB disease among IDUs has been shown to peak several years after HIV infection in both the pre-HAART[88] and post-HAART eras[85]. This time period represents an opportunity for prevention and treatment, but important barriers remain in the care of TB among drug users.

Barriers to Care and Treatment Adherence

The hallmark of TB control is the effective identification and treatment of cases, and drug users present a unique set of challenges for both. Studies have reported that IDUs have difficulty completing medical evaluations[27, 35, 95] or adhering to treatment for LTBI[35] or TB disease[96]. Even symptomatic IDUs have waited longer to present for treatment after TB symptom onset ("patient delay")[97], which can increase TB transmission rates or lead to more severe disease[98]. Furthermore, in a study of over 5,000 new AIDS cases in New York[99], patients with a history of injection drug use were 3.6 times more likely (95%CI 1.3–10.2) to have an opportunistic infection, including TB disease, at the time of AIDS diagnosis, further suggesting decreased care-seeking behavior among IDUs.

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

TB knowledge and perceptions may further impact care-seeking behavior[101]. In knowledge surveys, most IDUs understood they were at high risk for 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]. Perceptions that TB can be prevented by condom use or bleaching needles, reported in one study[20], suggest that HIV/AIDS education messages can be confused with TB prevention, a problem which itself has led to longer patient delay in some settings[104].

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

Even when barriers to healthcare access are overcome, adherence to long treatment regimens can be particularly problematic for drug users. Injection drug use [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 had the highest rates of both regulatory intervention and detention for treatment completion, and regulatory action was associated with both crack cocaine and injection drug use[111]. Finally, in a study of 96 South African patients who failed to complete treatment for MDR-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, with cutoffs of 10 mm for IDUs and 5 mm for HIV-seropositive individuals generally recommended[114], though the use of reduced cutoffs remains controversial[115–118]. Additional issues with TST include measurement reliability, the booster phenomenon (where an initial TST provides an immunologic stimulus that can lead to subsequent false positive tests), potential cross-reactivity among BCG-vaccinated individuals and anergic response in immunocompromised individuals. The CDC no longer recommends testing for cutaneous anergy in HIV-infected persons[119], following two randomized controlled trials which failed to demonstrate benefit of LTBI treatment for anergic individuals[120, 121]. After these trials, however, several observational studies demonstrated reduced incidence of TB disease among anergic individuals who underwent treatment for LTBI[19, 76, 122].

TST's requirement for return visits 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/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, Netherlands, establishment of a mobile unit providing chest radiographs for drug users and homeless persons contributed to a 50% decline of TB incidence in this group[126]. In most settings, however, TST remains the mainstay of targeted testing, though new methods demonstrate promise for improving case-finding among high-risk populations.

Interferon-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 *M. tuberculosis* antigens. Two diagnostic IGRAs are now commercially available – QuantiFERON®-TB Gold In-Tube (QFT-GIT, Cellestis, Victoria, Australia) and T-SPOT-TB (Oxford Immunotec, Abingdon, UK). The U.S. Centers for Disease Control and Prevention (CDC) has recommended the use of an earlier IGRA, QuantiFERON®-TB Gold, for all circumstances where TST is currently used[127]. IGRA advantages include insensitivity to BCG vaccination, the lack of a return visit and the absence of boosting, 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 utilized in several studies involving drug users. A study of over 1,000 IDUs in the endemic border city of Tijuana, Mexico found 67% LTBI prevalence using QFT-GIT[128]. Elsewhere, a study of crack cocaine smokers in Houston, Texas evaluated both QFT-G and T-Spot TB, finding LTBI prevalence of 34% with the IGRAs and 28% LTBI prevalence using TST[36]. Earlier studies comparing TST with a PPD-based IGRA (QuantiFERON®) found much higher LTBI prevalence using IGRAs (19%–65%) than TST (9–30%)[16, 26]. These results again demonstrate the high prevalence of LTBI and may suggest increased sensitivity of IGRAs among drug users, though further research and validation of the tests are needed.

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[129] and HIV-seropositive individuals[130]. Observational studies have shown decreased TB incidence among drug users after six[131, 132] and twelve[122] months of INH. Currently, the CDC recommends nine months of once-daily INH for HIV-negative individuals, with twice-weekly administration as directly observed therapy (DOT) an acceptable alternative[114].

A number of interventional studies have sought to identify methods for improving TB treatment adherence and completion in drug users. Drug treatment centers utilizing 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 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 offering incentives (Table 2),[142, 143] providing further justification for the integration of tuberculosis testing/treatment with other services for drug users[144–148].

Co-location of services can improve TB medication adherence and also drug treatment outcomes[149]; however, sustaining these gains may depend on continued drug rehabilitation. For example, 73% of patients in one study failed to complete LTBI treatment because they were discharged from the drug treatment program providing the medication[138]. Elsewhere, Casado and colleagues conducted a follow-up study of 131 HIV-seropositive individuals who had received nine months of LTBI treatment. TB disease developed in eight patients and was associated with continued drug abuse[150].

Fewer studies report on the treatment of TB disease among drug users, though high rates of treatment completion are reported in several studies which 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 linked to programs upon release from prison, 9 of 10 recovering addicts were able to complete treatment [157]. With 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 treatment completion[160]; this review, however, included only two studies conducted among IDUs which both used completion of LTBI treatment, and not TB disease as an endpoint[137, 139].

Special Treatment Considerations

A number of unique considerations exist for treating TB in patients who use illicit drugs. Standard TB treatment regimens including INH, rifampin and pyrazinamide can be hepatotoxic[161–163], an important consideration for IDUs who have high prevalence of chronic viral hepatitis[164, 165] and alcohol abuse[105]. In one study, patients with TB and co-infection with viral hepatitis or HIV were at a four- to five-fold increased risk for developing drug-induced hepatitis (DIH), and a 14-fold increased risk if co-infected with both[166]. DIH associated with anti-tuberculosis medications has been studied in several different settings[166–170], and while drug regimens and criteria for DIH have varied, the studies have uniformly established the safety of anti-tuberculosis drugs among individuals with viral hepatitis undergoing treatment for LTBI[167–169] and TB disease[166, 169, 170]. Among studies exploring predictive factors for DIH[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, 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 on opiate immunoassays[173, 174]. Concurrent treatment with rifampin/methadone is safe, though the dose of methadone may need to be increased[172]; nonetheless, in patients taking both drugs, rifampin has been frequently discontinued due to non-serious adverse reactions[175]. A related drug, rifabutin, is a less-potent inducer of hepatic enzymes[176] and was found in one 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 on HAART[178]. The effect of this drug on opiate immunoassays has not been studied to our knowledge.

Conclusions

Drug users remain a high risk group for TB infection and disease, and injection drug use has been an important factor in HIV-associated epidemics of TB worldwide. Treatment barriers, including poor adherence and limited access to care, pose unique challenges for drug users, while serving 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, geared toward sustaining positive outcomes.

The successful treatment of LTBI and TB disease among drug users has been demonstrated in a variety of settings. With close monitoring, special situations including methadone maintenance or co-infection with viral hepatitis, may also be managed successfully. Available evidence abundantly demonstrates improved treatment adherence for drug users when providing DOT, 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 high-risk groups such as drug users is an important part of an overall strategy which has likely contributed to the decrease in TB prevalence seen throughout the last decade in many countries. To sustain these gains, and to help arrest TB epidemics worldwide, continued attention must be paid to high-risk populations including drug users and IDUs.

Acknowledgments

At the time of this study, R.D. and T.R. were supported by a grant from the National Institute of Drug Abuse (T32DA023356). R.D. was additionally supported by an award from the Hispanic Serving Health Professions Schools. The authors report no conflicts of interest.

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. [PubMed: 10615718]

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 D. 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 D. 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. [PubMed: 16704834]
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. [PubMed: 17568852]
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. [PubMed: 16230316]
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. [PubMed: 18257988]
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. [PubMed: 17289861]
9. World Health Organization. UNAIDS and UN Office of Drugs and Crime. [Accessed September 8, 2008] 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.
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. [PubMed: 8589151]
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. [PubMed: 8100692]
12. Mathur ML, Chaudhary RC. Increased risk of tuberculosis in opium addicts. Indian J Med Sci. 1996; 50:365–7. [PubMed: 9057372]
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. [PubMed: 8596549]
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 Commun H. 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. [PubMed: 8994290]
16. Converse PJ, Jones SL, Astemborski J, Vlahov D, Graham NM. Comparison of a tuberculin interferon-gamma assay with the tuberculin skin test in high-risk adults: effect of human immunodeficiency virus infection. J Infect Dis. 1997; 176:144–50. [PubMed: 9207360]
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 D. 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. [PubMed: 9223727]
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 Resp 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. [PubMed: 9926545]
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. [PubMed: 9585747]
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. [PubMed: 9580534]

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. [PubMed: 9789160]
24. Alvarez Rodriguez M, Godoy Garcia P. Prevalence of tuberculosis and HIV infections among participants in an intravenous drug user risk-control program. Rev Esp Salud Public. 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. [PubMed: 10198656]
26. Kimura M, Converse PJ, Astemborski J, et al. Comparison between a whole blood interferon-gamma 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. [PubMed: 10191241]
27. Rusen ID, Yuan L, Millson ME. Prevalence of Mycobacterium tuberculosis infection among injection drug users in Toronto. CMAJ. 1999; 160:799–802. [PubMed: 10189423]
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 D. 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. [PubMed: 12690767]
30. Portilla J, Esteban J, Llinares R, et al. Prevalence of chronic hidden infections in a cohort of patients in substitutive treatment with methadone. Med Clin (Barc). 2001; 116:330–2. [PubMed: 11333762]
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(10):1183–90. [PubMed: 12410478]
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. [PubMed: 12006219]
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. [PubMed: 12238571]
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. [PubMed: 11937620]
35. Brassard P, Bruneau J, Schwartzman K, Senecal M, Menzies D. Yield of tuberculin screening among injection drug users. Int J Tuberc Lung D. 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 D. 2007; 11:1183–9.
37. Friedman H, Newton C, Klein TW. Microbial infections, immunomodulation, and drugs of abuse. Clin Microbiol Rev. 2003; 16:209. [PubMed: 12692094]
38. Wei G, Moss J, Yuan CS. Opioid-induced immunosuppression: is it centrally mediated or peripherally mediated? Biochem Pharmacol. 2003; 65:1761–6. [PubMed: 12781327]
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. [PubMed: 16142670]
40. Hudolin V. Tuberculosis and alcoholism. Ann N Y Acad Sci. 1975; 252:353–64. [PubMed: 1056734]
41. Barclay DM 3rd, Richardson JP, Fredman L. Tuberculosis in the homeless. Arch Fam Med. 1995; 4:541–6. [PubMed: 7773431]
42. Nelson S, Mason C, Bagby G, Summer W. Alcohol, tumor necrosis factor, and tuberculosis. Alcohol Clin Exp Res. 1995; 19:17–24. [PubMed: 7771645]
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. [PubMed: 16055879]
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 D. 2005; 9:430–6.

45. Niveau G. Prevention of infectious disease transmission in correctional settings: a review. Public Health. 2006; 120:33–41. [PubMed: 16129465]
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. [PubMed: 15047946]
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. [PubMed: 16903459]
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. [PubMed: 9498955]
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. [PubMed: 9145741]
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 D. 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. [PubMed: 8924259]
52. Rodrigo T, Cayla JA, Garcia de Olalla P, et al. Characteristics of tuberculosis patients who generate secondary cases. Int J Tuberc Lung D. 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. [PubMed: 9237715]
54. Chin DP, DeRiemer K, Small PM, et al. Differences in contributing factors to tuberculosis incidence in U.S. -born and foreign-born persons. Am J Respir Crit Care. 1998; 158:1797–803.
55. Inigo Martinez J, Chaves Sanchez F, Arce Arnaez A, et al. Recent transmission of tuberculosis in Madrid (Spain): usefulness of molecular techniques. Med Clin (Barc). 2000; 115:241–5. [PubMed: 11013145]
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 D. 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. [PubMed: 12197687]
58. FitzGerald JM, Fanning A, Hoepnner V, Hershfield E, Kunimoto D. The molecular epidemiology of tuberculosis in western Canada. Int J Tuberc Lung D. 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. [PubMed: 17064454]
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. [PubMed: 7993412]
61. Palmero D, Ritacco V, Ambroggi M, et al. Multidrug-resistant tuberculosis in AIDS patients at the beginning of the millennium. Medicina (B Aires). 2006; 66:399–404. [PubMed: 17137168]
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 D. 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. [PubMed: 11170771]
64. Conover C, Ridzon R, Valway S, et al. Outbreak of multidrug-resistant tuberculosis at a methadone treatment program. Int J Tuberc Lung D. 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. [PubMed: 9214250]
66. CDC. Crack cocaine use among persons with tuberculosis--Contra Costa County, California, 1987–1990. MMWR Morb Mortal Wkly Rep. 1991; 40:485–9. [PubMed: 2072883]

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. [PubMed: 7977929]
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 D. 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 D. 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. [PubMed: 16836841]
71. Perlman DC, Perkins MP, Paone D, et al. “Shotgunning” as an illicit drug smoking practice. J Subst Abuse Treat. 1997; 14:3–9. [PubMed: 9218230]
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. 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 D. 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. [PubMed: 426578]
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. [PubMed: 2915665]
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. [PubMed: 8100693]
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. [PubMed: 7794543]
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. [PubMed: 9377124]
79. Godoy P, Castilla J, Rullan JV. Incidence and risk factors of the association of AIDS and tuberculosis in Spain. Med Clin (Barc). 1998; 110:205–8. [PubMed: 9547731]
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(1):114–20. [PubMed: 9652430]
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. [PubMed: 11825115]
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 D. 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. [PubMed: 16288403]
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(5):633–41. [PubMed: 16897662]
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; 18:2521–7. [PubMed: 18025889]
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. [PubMed: 8605589]

87. Markowitz N, Hansen NI, Hopewell PC, et al. Incidence of tuberculosis in the United States among HIV-infected persons. The Pulmonary Complications of HIV Infection Study Group. Ann Intern Med. 1997; 126:123–32. [PubMed: 9005746]

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(8):1201–8. [PubMed: 12819522]

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. [PubMed: 10461317]

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. [PubMed: 11784470]

91. Perez-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. Med Clin (Barc). 1998; 110:167–70. [PubMed: 9547719]

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 D. 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. [PubMed: 9785679]

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. [PubMed: 14502020]

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. [PubMed: 8546549]

96. Pablos-Mendez A, Knirsch CA, Barr RG, Lerner BH, Frieden TR. Nonadherence in tuberculosis treatment: predictors and consequences in New York City. Am J Med. 102:164–70. [PubMed: 9217566]

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. [PubMed: 15230500]

98. Golub JE, Bur S, Cronin WA, et al. Delayed tuberculosis diagnosis and tuberculosis transmission. Int J Tuberc Lung D. 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. [PubMed: 17364409]

100. Morice AH, Menon MS, Mulrennan SA, et al. Opiate therapy in chronic cough. Am J Respir Crit Care. 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. [PubMed: 10194740]

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. [PubMed: 15587347]

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. [PubMed: 7604926]

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. [PubMed: 10930157]

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; (Suppl 3):S179–89. [PubMed: 16251816]

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. [PubMed: 8190855]

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. [PubMed: 15768335]

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(6):789–94. [PubMed: 10189422]

109. Gelmanova IY, Keshavjee S, Golubchikova VT, et al. Barriers to successful tuberculosis treatment in Tomsk, Russian Federation: non-adherence, default and the acquisition of multidrug resistance. Bull World Health Organ. 2007; 85:703–11. [PubMed: 18026627]

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. [PubMed: 9149565]

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. [PubMed: 9929527]

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 D. 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. [PubMed: 17339619]

114. CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. 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. [PubMed: 1727959]

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. 1996; 154(4 Pt 1): 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 D. 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. [PubMed: 16886159]

119. CDC. Anergy skin testing and tuberculosis [corrected] preventive therapy for HIV-infected persons: revised recommendations. Centers for Disease Control and Prevention. 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. [PubMed: 9233868]

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. [PubMed: 9295239]

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. [PubMed: 10546859]

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 D. 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 D. 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. [PubMed: 15482557]

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. 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. [PubMed: 16357824]

128. Garfein, RS.; Rodwell, T.; Brouwer, KC., et al. The First Global Symposium on Interferon-y Assays. Vancouver, BC Canada: 2007. 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.

129. Smieja MJ, Marchetti CA, Cook DJ, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. Cochrane Database Syst Rev. 2000; (2):CD001363. [PubMed: 10796642]

130. Woldehanna S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database Syst Rev. 2004; (1):CD000171. [PubMed: 14973947]

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. [PubMed: 8774208]

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. [PubMed: 14689352]

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. [PubMed: 12062463]

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. [PubMed: 8729149]

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. [PubMed: 10609595]

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. [PubMed: 10724056]

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. [PubMed: 11165450]

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. [PubMed: 10707445]

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. [PubMed: 11382368]

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. [PubMed: 18091290]

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 D. 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. 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. [PubMed: 11564856]

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. [PubMed: 10186640]

145. Foley ME, Ehr AP, Raza B, Devlin CJ. Tuberculosis surveillance in a therapeutic community. J Addict Dis. 1995; 14:55–65. [PubMed: 7632747]

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. [PubMed: 10857471]

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):iv24–33. [PubMed: 16107437]

148. Sylla L, Bruce RD, Kamarulzaman A, Altice FL. Integration and co-location of HIV/AIDS, tuberculosis and drug treatment services. Int J Drug Policy. 2007; 18:306–12. [PubMed: 17689379]

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. [PubMed: 7484335]

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. [PubMed: 11753825]

151. McDonald RJ, Memon AM, Reichman LB. Successful supervised ambulatory management of tuberculosis treatment failures. Ann Intern Med. 1982; 96:297–302. [PubMed: 7059091]

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. 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. [PubMed: 8712276]

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. [PubMed: 8958898]

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 D. 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 D. 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. [PubMed: 9817177]

158. Chaulk CP, Friedman M, Dunning R. Modeling the epidemiology and economics of directly observed therapy in Baltimore. Int J Tuberc Lung D. 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 D. 2007; 11:120–1.

160. Volmink J, Garner P. Directly observed therapy for treating tuberculosis. Cochrane Database Syst Rev. 2006; (2):CD003343. [PubMed: 16625579]

161. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. A meta-analysis. Chest. 1991; 99:465–71. [PubMed: 1824929]

162. Mitchell I, Wendon J, Fitt S, Williams R. Anti-tuberculous therapy and acute liver failure. Lancet. 1995; 345:555–6. [PubMed: 7786350]

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. [PubMed: 16392079]

164. Lemberg BD, Shaw-Stiffel TA. Hepatic disease in injection drug users. Infect Dis Clin North Am. 2002; 16:667–79. [PubMed: 12371121]

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. [PubMed: 17644020]

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. 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. [PubMed: 11641824]

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. [PubMed: 12539070]

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. [PubMed: 16679670]

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. [PubMed: 17356096]

171. Kreek MJ, Garfield JW, Gutjahr CL, Giusti LM. Rifampin-induced methadone withdrawal. N Engl J Med. 1976; 294:1104–6. [PubMed: 1256526]

172. Raistrick D, Hay A, Wolff K. Methadone maintenance and tuberculosis treatment. BMJ. 1996; 313:925–6. [PubMed: 8876100]

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. [PubMed: 9638350]

174. Daher R, Haidar JH, Al-Amin H. Rifampin interference with opiate immunoassays. Clin Chem. 2002; 48:203–4. [PubMed: 11751562]

175. Cook SV, Fujiwara PI, Frieden TR. Rates and risk factors for discontinuation of rifampicin. Int J Tuberc Lung D. 2000; 4:118–22.

176. Blaschke TF, Skinner MH. The clinical pharmacokinetics of rifabutin. Clin Infect Dis. 1996; 22(Suppl 1):S15–21. [PubMed: 8785251]

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. [PubMed: 8957145]

178. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: principles of therapy and revised recommendations. Centers for Disease Control and Prevention. 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. [PubMed: 16840411]

Clin Infect Dis. Author manuscript; available in PMC 2011 June 08.

Table 1

Summary of studies reporting prevalence of positive tuberculin skin test (TST) among drug users, 1995–2008 (minimum 50 subjects)

Study	City	Subjects (#TST results)	TST Criteria	TST+ %	Cutaneous Anergy %	Predictive Factors	HIV+ %
Reyes 1996[15]	San Juan, Puerto Rico	716 (611) drug users	NR	10	30	HIV+ Injection drug use History of incarceration/ residential drug treatment	35
Converse 1997[16]	Baltimore, Maryland	66 (NR) IDUs	10 mm; 5 mm if HIV-positive	30	23	NR	52
Lifson 1997[17]	Denver, Portland, San Francisco, Oakland	1079 (997) IDUs	10 mm; 5 mm if HIV-positive	13	NR	Race/ethnicity Age group City	9.5
Strathdee 1997[18]	Vancouver, British Columbia	1006 (NR) IDUs	NR	25	NR	Not reported	23
Daley 1998[19]	San Francisco, California	1109 (NR) IDUs	10 mm; 5 mm if HIV-positive	39	10	NR	32
Durante 1998[20]	New Haven, Connecticut	786 (662) drug users	10 mm; 5 mm if HIV-positive	16	12	Older age Non-white race History of injection drug use Foreign birth	8[d]
Malotte 1998[21]	Long Beach, California	1004 (782) drug users	5 mm	18	NR	Older age Non-white race/ ethnicity Male gender	4
Robles 1998[22]	San Juan, Puerto Rico	464 (424) IDUs	10 mm; 5 mm if HIV-positive	17	31	NR	43
Taubes 1998	New York	147 (137) mentally ill drug users	10 mm	31	NR	Recent crack cocaine use Schizophrenia	19
Alvarez Rodriguez 1999[24]	Lleida, Spain	150 (NR) drug users	5 mm; 15 mm if BCG-vaccinated	27	NR	History of incarceration	36
Malotte 1999[25]	Long Beach, California	1078 (777) drug users	5 mm	21	NR	History of TB exposure	3
Kimura 1999[26]	Baltimore, Maryland	1008 (467) IDUs	10 mm; 5 mm if HIV-positive	19	NR	NR	36
Rusen 1999[27]	Toronto, Ontario	167 (155) IDUs	5 mm and 10 mm	31 (5 mm) 28 (10 mm)	0	Birth outside Canada Age ≥ 35	4.7[d]
Salomon 2000[28]	New York	610 (566) IDUs	10 mm; 5 mm if HIV-positive/ unknown	15	9	History of TST positivity Age/Duration of IDU[b]	21[d]
Askarian 2001[29]	Shiraz, Iran	319 drug users	10 mm	40	NR	Age Male gender Injection drug use	NR
Portilla 2001[30]	Alicante, Spain	189 (NR) drug users	5 mm	59	NR	Older age	29
Howard 2002[31]	Bronx, New York	806 (793) heroin users	10 mm; 5 mm if HIV-positive	25	16	Separately reported for HIV +/HIV− subjects[c]	32
Portu 2002[32]	Basque Region, Spain	1,131 (NR) IDUs	5 mm	42	NR	HIV-seronegativity	47

Study	City	Subjects (#TST results)	TST Criteria	TST+ %	Cutaneous Anergy %	Predictive Factors	HIV+ %
Quaglio 2002[33]	Italy (city not specified)	252 (237) drug users	5 mm and 10 mm	26 (5 mm) 11 (10 mm)	NR	NR	21
Riley 2002[34]	Baltimore, Maryland	286 (241) IDUs	Not reported	17	NR	Longer smoking history Difficulty acquiring food Self-reported HIV+	18[d]
Brassard 2004[35]	Montreal, Quebec	262 (246) IDUs	5 mm	22	NR	Older age at first injection Duration of IDU HIV−	24
Grimes 2007[36]	Houston, Texas	123 (99) crack cocaine users	10 mm; 5 mm if HIV-positive	28	NR	Crack cocaine use at home	7

[a] Abbreviations: IDU (injection drug use), NR (not 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, African American race, 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, higher CD4 count.

[d] Self-reported.

Table 2

Summary of studies demonstrating elevated risk for TB among injection drug users (IDUs) compared with other HIV risk categories[a]

Study	Study Methods	Number of subjects	Country	Period of study	Selected findings
Markowitz 1993[11]	Multicenter cross-sectional study	1,171 HIV+ patients	USA	1988–1990	IDUs more likely to be TST-positive than MSM (15% vs 2.5%, $P < 0.001$
Moreno 1993[76]	Retrospective cohort study	706 HIV+ patients	Spain	1985–1989	TB more frequent among IDUs with no previous INH treatment (63/290, 22%) than among patients in other HIV transmission categories (0/60, 0%).
Castilla 1995[77]	National surveillance data analysis	22445 AIDS cases	Spain	1988–1993	Highest proportions of extrapulmonary TB at AIDS diagnosis among HIV transmission (35%) observed for IDUs
Gollub 1997[78]	Analysis of surveillance data of Philadelphia, Pennsylvania	74 cases of TB disease in AIDS registry	USA	1993	IDUs or individuals acquiring HIV through heterosexual sex are more likely to have TB disease than MSM (OR 3.3; 95% CI 1.3, 8.4)
Godoy 1998[79]	National surveillance data analysis	2,826 HIV/TB cases	Spain	1994	IDU is an independent predictor of TB among AIDS cases (OR = 1.4; CI 95%, 1.2–1.6).
Jones 1998[80]	Medical records analysis from 9 U.S. cities	15,588 MSM and 14,475 IDUs	USA	1991–1996	Higher incidence of TB cases among IDUs than MSM
Morgello 2002[81]	Retrospective analysis of autopsy data	394 HIV-infected adults	USA	1979–2000	Tuberculosis associated with injection drug use but not sexual risk
Calpe 2004[82]	Analysis of surveillance data of Valencia, Spain	459 TB cases	Spain	1987–2001	59% of HIV+ TB cases were attributable to drug use
Girardi 2005[180]	Multicenter prospective cohort study	22,217 HIV+ patients	Multiple[b]	1996–2003	TB rate lower for MSM than IDUs (RR, 2.46; 95% CI 1.51–4.01)
Podlekareva 2006[84]	EuroSIDA surveillance data	24,991 AIDS cases	Multiple[c]	1994–2005	Injection drug use, and not CD4+ count, predicted risk for TB among patients with CD4+ counts ≥ 300 cells/μL (OR 2.1; 95%CI, 1.1–4.2)
Muga 2007[85]	Multicenter cohort study	2238 HIV sero-converters	Spain	1980–2004	IDUs more likely to develop tuberculosis (RH 3.0; 95% CI, 1.72–5.26, P < 0.001).

[a]Abbreviations: IDU (injection drug user); MSM (men who have sex with men); RR (relative risk); OR (odds ratio); RH (relative hazard); CI (confidence interval).

[b]1.3 European and North American cohort studies.

[c]28 European countries, Argentina and Israel.

Table 3

Cost-benefit analyses for treatment of Latent TB Infection (LTBI) among drug users[a]

Study	Setting	Number of patients in model	Incentives incorporated into model?	Number of patients completing treatment/number of eligible patients	Estimated no. of cases of TB prevented/Time period	Projected net cost savings
Gourevitch 1998[141]	MTP	507	No	151/184	11/5 yrs	$285,284/5 yrs[b]
Snyder 1999[142]	MTP	2,689	Yes	285/378	30/10 yrs	$104,660/10 yrs
Perlman 2001[143]	SEP	1,000[c]	Yes	175/175*	3/5 yrs	$46,226/5 yrs

[a]MTP = methadone treatment program; SEP = syringe exchange program.

Clin Infect Dis. Author manuscript; available in PMC 2011 June 08.