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
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]. "Shot-gunning," 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>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Location</th>
<th>Study subjects</th>
<th>No. of TST results</th>
<th>TST criteria</th>
<th>Positive TST result, %</th>
<th>Cutaneous anergy, %</th>
<th>Predictive factors</th>
<th>Positive for HIV infection, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reyes et al. [15]</td>
<td>1996</td>
<td>San Juan, Puerto Rico</td>
<td>716 Drug users</td>
<td>611</td>
<td>NR</td>
<td>10</td>
<td>30</td>
<td>Positive for HIV infection, IDU, history of incarceration, residential drug treatment</td>
<td>35</td>
</tr>
<tr>
<td>Converse et al. [16]</td>
<td>1997</td>
<td>Baltimore, MD</td>
<td>66 IDUs</td>
<td>NR</td>
<td>10 mm; 5 mm if HIV positive</td>
<td>30</td>
<td>23</td>
<td>NR</td>
<td>52</td>
</tr>
<tr>
<td>Lifson et al. [17]</td>
<td>1997</td>
<td>Denver, CO; Portland, ME; San Francisco, CA; Oakland, CA</td>
<td>1079 IDUs</td>
<td>997</td>
<td>10 mm; 5 mm if HIV positive</td>
<td>13</td>
<td>NR</td>
<td>Race/ethnicity, age group, city of residence</td>
<td>10</td>
</tr>
<tr>
<td>Strathdee et al. [18]</td>
<td>1997</td>
<td>Vancouver, BC</td>
<td>1006 IDUs</td>
<td>NR</td>
<td>NR</td>
<td>25</td>
<td>NR</td>
<td>NR</td>
<td>23</td>
</tr>
<tr>
<td>Daley et al. [19]</td>
<td>1998</td>
<td>San Francisco, CA</td>
<td>1109 IDUs</td>
<td>NR</td>
<td>10 mm; 5 mm if HIV positive</td>
<td>30</td>
<td>10</td>
<td>NR</td>
<td>32</td>
</tr>
<tr>
<td>Dusart et al. [20]</td>
<td>1998</td>
<td>New Haven, CT</td>
<td>786 Drug users</td>
<td>662</td>
<td>10 mm; 5 mm if HIV positive</td>
<td>16</td>
<td>12</td>
<td>Older age, nonwhite ethnicity; history of IDU, foreign birth</td>
<td>6</td>
</tr>
<tr>
<td>Malotte et al. [21]</td>
<td>1998</td>
<td>Long Beach, CA</td>
<td>1006 Drug users</td>
<td>782</td>
<td>5 mm</td>
<td>18</td>
<td>NR</td>
<td>Older age, nonwhite ethnicity, male sex</td>
<td>4</td>
</tr>
<tr>
<td>Robles et al. [22]</td>
<td>1998</td>
<td>San Juan, Puerto Rico</td>
<td>464 IDUs</td>
<td>424</td>
<td>10 mm; 5 mm if HIV positive</td>
<td>17</td>
<td>31</td>
<td>NR</td>
<td>43</td>
</tr>
<tr>
<td>Taubes et al. [23]</td>
<td>1998</td>
<td>New York, NY</td>
<td>147 Mentally ill drug users</td>
<td>137</td>
<td>10 mm</td>
<td>31</td>
<td>NR</td>
<td>Recent crack cocaine use, schizophrenia</td>
<td>19</td>
</tr>
<tr>
<td>Alvarez Rodriguez et al. [24]</td>
<td>1999</td>
<td>Lleida, Spain</td>
<td>150 Drug users</td>
<td>NR</td>
<td>5 mm; 15 mm if BCG vaccinated</td>
<td>27</td>
<td>NR</td>
<td>History of incarceration</td>
<td>36</td>
</tr>
<tr>
<td>Malotte et al. [25]</td>
<td>1999</td>
<td>Long Beach, CA</td>
<td>1078 Drug users</td>
<td>777</td>
<td>5 mm</td>
<td>21</td>
<td>NR</td>
<td>History of TB exposure</td>
<td>3</td>
</tr>
<tr>
<td>Kimura et al. [26]</td>
<td>1999</td>
<td>Baltimore, MD</td>
<td>1008 IDUs</td>
<td>467</td>
<td>10 mm; 5 mm if HIV positive</td>
<td>19</td>
<td>NR</td>
<td>NR</td>
<td>36</td>
</tr>
<tr>
<td>Rusen et al. [27]</td>
<td>1999</td>
<td>Toronto, ON</td>
<td>167 IDUs</td>
<td>196</td>
<td>5 mm and 10 mm</td>
<td>31</td>
<td>16</td>
<td>Birth outside Canada, age ,35 years</td>
<td>5</td>
</tr>
<tr>
<td>Salmon et al. [28]</td>
<td>2000</td>
<td>New York, NY</td>
<td>610 IDUs</td>
<td>566</td>
<td>10 mm; 5 mm if HIV positive</td>
<td>15</td>
<td>9</td>
<td>History of TST positivity, age, duration of IDU</td>
<td>21a</td>
</tr>
<tr>
<td>Askarian et al. [29]</td>
<td>2001</td>
<td>Shiraz, Iran</td>
<td>319 Drug users</td>
<td>...</td>
<td>10 mm</td>
<td>40</td>
<td>NR</td>
<td>Age, male sex, IDU</td>
<td>NR</td>
</tr>
<tr>
<td>Portila et al. [30]</td>
<td>2001</td>
<td>Alicante, Spain</td>
<td>189 Drug users</td>
<td>NR</td>
<td>5 mm</td>
<td>59</td>
<td>NR</td>
<td>Older age</td>
<td>29</td>
</tr>
<tr>
<td>Howard et al. [31]</td>
<td>2002</td>
<td>Bronx, NY</td>
<td>806 Heroin users</td>
<td>793</td>
<td>10 mm; 5 mm if HIV positive</td>
<td>25</td>
<td>16</td>
<td>Separately reported for HIV positive and HIV negative subjects</td>
<td>32</td>
</tr>
<tr>
<td>Pont et al. [32]</td>
<td>2002</td>
<td>Basque region, Spain</td>
<td>1131 IDUs</td>
<td>NR</td>
<td>5 mm</td>
<td>42</td>
<td>NR</td>
<td>HIV seronegativity</td>
<td>47</td>
</tr>
<tr>
<td>Quaglio et al. [33]</td>
<td>2002</td>
<td>Italy (city not specified)</td>
<td>252 Drug users</td>
<td>237</td>
<td>5 mm and 10 mm</td>
<td>26</td>
<td>21 (10 mm)</td>
<td>NR</td>
<td>42</td>
</tr>
<tr>
<td>Riley et al. [34]</td>
<td>2002</td>
<td>Baltimore, MD</td>
<td>286 IDUs</td>
<td>241</td>
<td>NR</td>
<td>17</td>
<td>NR</td>
<td>Longer smoking history, difficulty acquiring food, self-reported HIV infection</td>
<td>18a</td>
</tr>
<tr>
<td>Brassard et al. [35]</td>
<td>2004</td>
<td>Montreal, PQ</td>
<td>262 IDUs</td>
<td>246</td>
<td>5 mm</td>
<td>22</td>
<td>NR</td>
<td>Older age at first injection, duration of IDU, HIV negative</td>
<td>24</td>
</tr>
<tr>
<td>Grimes et al. [36]</td>
<td>2007</td>
<td>Houston, TX</td>
<td>123 Crack cocaine users</td>
<td>99</td>
<td>10 mm; 5 mm if HIV positive</td>
<td>28</td>
<td>NR</td>
<td>Crack cocaine use at home</td>
<td>7</td>
</tr>
</tbody>
</table>

**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.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study type</th>
<th>Study subjects</th>
<th>Country</th>
<th>Study date(s)</th>
<th>Selected findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Markowitz et al. [11]</td>
<td>1993</td>
<td>Multicenter cross-sectional</td>
<td>1171 HIV-positive patients</td>
<td>United States</td>
<td>1988–1990</td>
<td>IDUs more likely than MSM to have positive TST results (15% vs. 2.5%; (P &lt; .001))</td>
</tr>
<tr>
<td>Moreno et al. [76]</td>
<td>1993</td>
<td>Retrospective cohort study</td>
<td>706 HIV-positive patients</td>
<td>Spain</td>
<td>1985–1989</td>
<td>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%)</td>
</tr>
<tr>
<td>Castilla et al. [77]</td>
<td>1995</td>
<td>National surveillance data analysis</td>
<td>22,445 Patients with AIDS</td>
<td>Spain</td>
<td>1988–1993</td>
<td>Highest proportions of extrapulmonary TB at AIDS diagnosis among HIV transmission categories (35%) observed for IDUs</td>
</tr>
<tr>
<td>Gollub et al. [78]</td>
<td>1997</td>
<td>Analysis of surveillance data of Philadelphia, PA</td>
<td>74 Cases of TB disease in AIDS registry</td>
<td>United States</td>
<td>1993</td>
<td>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)</td>
</tr>
<tr>
<td>Godoy et al. [79]</td>
<td>1998</td>
<td>National surveillance data analysis</td>
<td>2826 Patients with HIV and TB coinfection</td>
<td>Spain</td>
<td>1994</td>
<td>IDU is an independent predictor of TB among patients with AIDS (OR, 1.4; 95% CI, 1.2–1.6)</td>
</tr>
<tr>
<td>Jones et al. [80]</td>
<td>1998</td>
<td>Medical-records analysis from 9 US cities IDUs</td>
<td>15,588 MSM and 14,475 IDUs</td>
<td>United States</td>
<td>1991–1996</td>
<td>Higher incidence of TB cases among IDUs than among MSM</td>
</tr>
<tr>
<td>Calpe et al. [82]</td>
<td>2004</td>
<td>Analysis of surveillance data of Valencia, Spain</td>
<td>459 Patients with TB</td>
<td>Spain</td>
<td>1987–2001</td>
<td>59% of HIV-positive study patients had TB that was attributable to drug use</td>
</tr>
<tr>
<td>Girardi et al. [83]</td>
<td>2005</td>
<td>Multicenter prospective cohort study</td>
<td>22,271 HIV-positive patients</td>
<td>Multiple*</td>
<td>1996–2003</td>
<td>TB rate lower for MSM than for IDUs (RR, 2.46; 95% CI, 1.51–4.01)</td>
</tr>
<tr>
<td>Podlekareva et al. [84]</td>
<td>2006</td>
<td>EuroSIDA surveillance data</td>
<td>24,991 Patients with AIDS</td>
<td>Multiple†</td>
<td>1994–2005</td>
<td>IDU, not CD4+ cell count, predicted risk of TB among patients with CD4+ cell counts &gt;300 cells/L (OR, 2.1; 95% CI, 1.1–4.2)</td>
</tr>
<tr>
<td>Muga et al. [85]</td>
<td>2007</td>
<td>Multicenter cohort study</td>
<td>2238 HIV seroconverters</td>
<td>Spain</td>
<td>1980–2004</td>
<td>IDUs more likely to develop TB (RH, 3.0; 95% CI, 1.72–5.26; (P &lt; .001))</td>
</tr>
</tbody>
</table>

**NOTE.**  
- MSM, men who have sex with men; RH, relative hazard; RR, relative risk.  
- *Includes 13 European and North American cohort studies.  
- †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.

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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 IGRA 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.

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