Re-examining treatment of latent tuberculosis infection

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In April 2000, the American Thoracic Society published guidelines for targeted tuberculin testing and the treatment of latent tuberculosis infection (LTBI) (1). These guidelines are a joint statement of the American Thoracic Society and the Centers for Disease Control and Prevention, and were endorsed by both the Infectious Diseases Society of America and the American Academy of Pediatrics. Similar recommendations were published by the Infectious Diseases Society of America in its guidelines for the treatment of tuberculosis (TB) (2). These updated guidelines were developed in recognition of the importance of treating LTBI as one component of eliminating TB in the United States – a goal reiterated in 1999 by the Advisory Council for the Elimination of Tuberculosis (3) – but also realizing the differing risks and benefits of treatment for patients based on their individual risks of developing active disease or drug toxicity (4). The 2000 edition of the *Canadian Tuberculosis Standards* provided similar recommendations for the treatment of LTBI (formerly known as chemoprophylaxis) and reminded us of the two major Canadian TB elimination initiatives: the National Tuberculosis Elimination Strategy (Medical Services Branch, 1992), with the aim of eliminating TB in First Nations people by 2010, and the National Consensus Conference on Tuberculosis (Health Canada, 1997), with an interim goal of a 5% reduction in the number of TB cases each year in Canada (5). Given the recent publication of the American guidelines and the updated *Canadian Tuberculosis Standards* (Fifth Edition), it was considered timely to remind readers of the evidence supporting the use of antituberculous chemotherapy in the treatment of latent infection.

Worldwide, there were an estimated 8.4 million new TB cases in 1999, with 80% of all new cases coming from 23 high incidence countries (6). In high incidence countries, TB elimination is focused on identification and directly observed therapy of individuals with active disease. Since its resurgence between 1985 and 1992 (with a peak of 26,673 cases), the number of cases of TB in the United States has decreased each year, with 18,361 (6.8 of 100,000) reported in 1998 (3). During the latter decade, the epidemiology has shifted, such that 42% of cases in 1998 occurred in foreign-born persons (3). The TB rate in Canada has been stable since 1987 at just under six of 100,000 (7). Similar to the United States, foreign-born cases account for an increasing proportion of TB in Canada: 64% in 1998 compared with 37% in 1981. The leading countries of origin of foreign-born TB cases in Canada are Vietnam, China, the Philippines, India, Hong Kong, Somalia, Haiti, Ethiopia, Sri Lanka, Pakistan and Poland (7). Canadian Aboriginals account for 15% of active TB (7), with cases largely confined to Manitoba, Saskatchewan and the Northwest Territories (8).

Targeted screening and treatment of LTBI require identification of those most at risk for active disease who would, therefore, benefit most from treatment. Co-infection with HIV is the greatest risk for active TB (1,9,10). Each year, 7% to 10% of HIV-infected individuals with a positive tuberculin skin test (TST) develop active TB (10-12). Globally, TB is the most common cause of death in HIV-infected individuals. There are limited data on TB and HIV co-infection in Canada. Of the cumulative Canadian AIDS cases to the end of 1996, 4.2% also had TB, with these patients more likely to have come from endemic countries (7). Other risk factors for developing active TB in those with a positive TST are recent TB infection (1), injection drug use (11,12) and homelessness (13). *The Medical Post* recently reported on the high rate of TB in Vancouver's east side, where it is estimated that 2000 residents have LTBI; this is attributed to poverty and over-

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crowding (14). A number of clinical conditions other than HIV are also associated with an increased risk of developing active TB. These entities and their relative risks are silicosis (30.0), diabetes mellitus (2.0 to 4.0), chronic renal failure and/or hemodialysis (10.0 to 25.3), gastrectomy (2.0 to 5.0), jejunoileal bypass (27.0 to 63.0), solid organ transplantation (20.0 to 74.0) and carcinoma of the head or neck (16.0) (1). Individuals with a positive TST and radiographic findings consistent with prior pulmonary TB also have a higher rate of active disease – 14.3 of 1000 persons over five years of follow-up in one study (15).

Even in the absence of co-infection with HIV, foreign-born persons are a group at increased risk for TB in both the United States and Canada (3,7,16-19). This risk varies according to whether the immigrant is from a high or low incidence country (7,17,18). Studies in both the United States and Canada have found that the majority of immigrants with TB are diagnosed within five years after arrival (17-19). Zuber et al (17) reported that almost 45% of active cases in immigrants were among those younger than 35 years of age but that the incidence remained high among persons originating from high prevalence areas, even several years after arrival. The risk of developing TB in long term residents correlated with a longer lifetime experience overseas (17). Currently, Canadian Citizenship and Immigration screening for TB extends to all persons who are applying to become legal landed immigrants or to obtain refugee status, visitors for six months or longer who have been in an endemic area for six months or longer, and visitors intending to work in an occupation where protection of public health is essential (20). The screening consists of a clinical evaluation and chest film (for those older than 11 years of age). Individuals with active TB are not allowed to enter Canada until treatment has been completed. Those with inactive pulmonary TB are supposed to be referred to Public Health for follow-up after arrival in Canada. TST is not part of routine surveillance. Loopholes in the system have been identified. Great variability in the quality of diagnostic processes and policies, as well as occasional deliberate fraud, have been identified as shortcomings in the United States program (21). In British Columbia, 20% of TB in immigrants occurred in persons who were not legally landed immigrants (students, visitors) and, hence, were not screened (18). A Queen's University study has found that federal government notification of provincial public health authorities of immigrants at risk for TB may be suboptimal (22).

Clinical trials examining the benefit of isoniazid (INH) for the treatment of LTBI date back to the 1950s. One of the first studies was a placebo controlled trial in 2750 asymptomatic children who were TST positive (23). There was a statistically significant decrease in extrapulmonary complications of TB in those who received INH (0.4%) compared with those who received a placebo (2.4%), as well as a trend toward benefit in preventing pulmonary disease (2.6% in treated versus 3.8% in controls). The benefit was maintained over two years of follow-up after treatment was completed. In the late 1950s and early 1960s, the United States Public Health Service undertook several large, one-year trials of INH for the treatment of LTBI in high risk populations: patients in mental institutions (24), household contacts of confirmed active TB cases (25) and villagers in Alaska (26). All trials were placebo controlled with randomization to wards or households rather than individual patients. Study subjects were not necessarily TST positive. In each of these trials, there was a statistically significant decrease in the occurrence of active pulmonary TB in subjects randomized to receive INH (24-26). The rates for household contacts were reduced from 0.49% to 0.11% (25), for those in mental institutions from 0.17% to 0.03% (24) and for the Alaskan villagers from 4.5% to 0.5% (26). The study involving the Alaskan villagers found that the benefit was maintained 19 years after treatment ended (27). The study involving household contacts also showed that one year of INH was successful in preventing primary TB infection and extrapulmonary TB in children (25).

Most subsequent studies have confirmed the benefit of one year of INH for the treatment of LTBI. One of the largest studies (27,830 TST-positive subjects) compared various treatment durations with placebo in persons with fibrotic pulmonary lesions compatible with previous TB (15). Compared with placebo, one year of INH reduced the risk of active TB by 75%, and 12 weeks reduced it by 65%. After five years of follow-up, the benefit of each INH regimen outweighed its risks. A trial of three different regimens (INH for six months, rifampin for three months or a combination of the two for six months) compared with placebo in Chinese men with silicosis (94% TST-positive) halved the rate of pulmonary TB, with no significant difference between the three regimens (28). Although providing benefit, it was somewhat modest, suggesting that longer treatment regimens may be more effective, at least in individuals with silicosis. Two nonrandomized trials of rifampin with or without INH in patients receiving directly observed therapy (using historical controls for comparison) found low rates of active TB in the treated group (0.9/1000 patient-years [29] and no cases [30]). A nonrandomized study of treatment in homeless individuals in Boston, Massachusetts who were recent TST converters also found that rifampin with or without INH for four to six months was effective in preventing development of active disease in 86 patients over a mean of 28.5 months of follow-up (13). TB developed in 8% of individuals who received no therapy or INH alone; this was in the context of an outbreak of INH-resistant TB, and the three INH treatment failures all had INH-resistant isolates, suggesting primary drug resistance as the cause for the INH failures (13).

The past decade has seen a number of studies from many countries evaluating various drug regimens for treating LTBI in HIV-infected individuals. The potential benefit of preventive therapy in HIV-infected individuals was first suggested by observational studies in injection drug users (11,12,31). Selwyn et al (12) reported that no patient who received LTBI treatment (over 173 person-years of follow-up) developed

active TB compared with 6.6/100 person-years for those not taking treatment (12). In another study, individuals who completed nine months of INH had 45% protection over three to 27 months of follow-up (31).

Randomized trials of treatment for LTBI in HIV infection have looked at a variety of regimens, with treatment courses ranging from two to six months. A placebo controlled trial of INH for six months in Haitian HIV-infected subjects found a 71% reduction in active TB for the entire group and an 83% reduction for the subgroup who were TST positive (32). Prophylaxis also had a protective effect in delaying progression to AIDS and death in the whole population and the TST-positive individuals (32). Similar benefits were not seen in the TST-negative group, but sample size was insufficient to detect a difference between the two treatment groups. A study of Ugandan HIV-infected adults showed that six months of INH reduced the risk of TB by 67% in TST-positive subjects (33). Benefit was not seen in anergic individuals (33). No statistically significant benefit was seen in subjects randomized to INH and rifampin or INH, rifampin and pyrazinamide for three months (33). More recently, one study found that two months of daily rifampin and pyrazinamide was similar in efficacy to nine months of INH in HIV-infected subjects who were TST positive, with a mean follow-up of 37 months (34).

Not all studies have demonstrated benefit. Halsey et al (35) found that twice weekly INH treatment for six months or twice weekly rifampin and pyrazinamide for two months produced only a modest, nonsustained benefit, so that during the second year of follow-up, TB rates were not significantly lower in the treatment groups. A study of INH for six months in Kenyan HIV-infected subjects showed no benefit, even in those who were TST positive (36). While six months of twice weekly INH or three months of twice weekly rifampin and pyrazinamide were effective in preventing TB in Zambian adults (with the greatest effect in those with a positive TST and higher lymphocyte counts), efficacy did wane with time (9). The studies in which benefit waned or was not seen all raised questions about the trial's ability to detect treatment differences, the role of reinfection, adherence and the optimal duration of treatment for LTBI.

Over the years, concerns have been raised repeatedly about the safety of INH, the problem of adherence to lengthy treatment durations and the possibility that treatment of LTBI promotes emergence of drug-resistant strains. There is no doubt about the importance of adherence. A placebo controlled study in Japan in which compliance was less than 50% in the treatment group found no benefit for subjects randomized to 12 months of INH (37). Studies have suggested that protection is better among those who took therapy as recommended (12,24,25,31). Likewise, there is no doubt that patients have difficulty completing a 12-month regimen. Many studies have demonstrated poor adherence; this is usually similar for placebo and active treatment arms, and worsens with increasing duration of treatment, supporting the notion that poor adherence is related more to duration of therapy than to the drug (15,23,24,33,36,37). Most studies evaluating treatment of LTBI sought culture confirmation of failures. Several studies commented that there was no evidence of selection for resistant strains (10,13,24,26,28).

Early trials using INH in the treatment of LTBI suggested that it was a very safe drug with no appreciable toxicity (24-26). With wider use, it was predictable that cases of INH-related toxicity, including serious adverse events, would be reported. In February 1970, 2321 employees on Capitol Hill in Washington, DC began a course of INH after the diagnosis of active TB in coworkers (38). In the ensuing months, 19 employees (8.2 of 1000) developed clinical signs of liver disease, and two died (one of pneumonia complicating hepatic coma and the other of ruptured varices). While the diagnostic criteria were not rigorous (a history of signs of jaundice or dark urine was acceptable), there were findings suggesting that employees taking INH developed hepatitis more often than coworkers not on INH (0.5 of 1000). Nine developed hepatitis within the first two months, and 11 were hospitalized. In 1972, eight deaths (57.9 of 100,000 completed treatment courses) due to hepatotoxicity (seven in one city) occurred in subjects enrolled in a surveillance program designed to monitor INH toxicity (39). The authors found that the risk of hepatitis was age related: zero/1000 in those younger than age 20 years, three/1000 in those aged 20 to 34 years, 12/1000 in those aged 35 to 49 years, 23/1000 in those between ages 50 and 64 years, and eight/1000 in those older than age 64 years. Nearly one-half of cases occurred by the third month, and three-quarters occurred by the sixth month; drinkers had higher rates than nondrinkers (39). Snider and Caras (40) carefully examined the literature, and state and national databases from 1965 to 1989 to identify reported deaths due to LTBI treated INH-associated hepatitis. They found 177 cases (23.2 of 100,000 treatment courses completed). Sixty per cent of cases were in individuals older than age 50 years. The number of cases decreased over the study years. This review suggested that women, especially those in the postpartum period, may be at increased risk (40). The International Union Against Tuberculosis (IAUT) trial, involving 27,830 patients, reported a 0.5% incidence of hepatitis, with three deaths (0.14 of 1000) (15). More recently, a prospective cohort study of patients receiving INH for LTBI found that 11 of 11,141 patients developed hepatotoxic reactions (0.1% of those starting and 0.15% of those completing treatment) (41). The rate increased with age, and there were trends toward increased rates in women and white individuals. However, only one patient required hospitalization, and all patients recovered without sequelae. Trials of INH in HIV-infected individuals have shown that hepatitis rates are low, with no INH-related deaths (31,33-35). These recent studies suggest that INH can be safely administered when patients are monitored closely.

The evidence would support a benefit for the treatment of LTBI in individuals at higher risk for active disease and that this benefit persists after the treatment course is completed. For single-drug therapy, a longer treatment course provides more benefit than a short course, although there is not a sta-

tistically significant difference between nine and 12 months' duration. More recent studies suggest that shorter courses of combination therapy may be equivalent to a longer course of INH and help address the very real problem of adherence. While the potential for INH hepatotoxicity must always be kept in mind, its incidence is probably not as high as reported in the 1970s, provided that patients are appropriately monitored. Eradication of TB remains an achievable and worthwhile goal.

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