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Treatment of latent tuberculosis infection: An update

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ABSTRACT

Isoniazid (INH) has been the mainstay of treatment of latent tuberculosis infection for almost 50 years. The currently recommended preferred regimen is 9 months daily self-administered INH (9H); this has efficacy of more than 90% if completed properly. Unfortunately, INH is associated with serious adverse events, including hepatotoxicity. Although risk factors for this complication are well established, allowing for better selection of candidates for therapy, this complication still occurs, and is occasionally fatal. Hence close follow up of patients is necessary, increasing the cost and complexity of treatment. This problem, plus the lengthy duration, results in poor acceptance by patients and providers, and poor adherence by patients. As a result, many preventable cases of tuberculosis continue to occur, and the public health impact of latent tuberculosis infection treatment is suboptimal. These problems have spurred interest in finding shorter, safer and cheaper alternative regimens, with similar efficacy. Of the many regimens that have been examined, 2 months of rifampin and pyrazinamide has excellent efficacy—in experimental studies in mice and randomized trials, largely in HIV-infected persons. However, while the safety of 2 months of rifampin and pyrazinamide appears acceptable in HIV-infected persons and children, in non-HIV-infected adults this regimen is associated with an unacceptably high rate of severe liver toxicity. Three to four months of INH and rifampin has had equivalent effectiveness as 6 months INH in several randomized trials. However, completion of therapy and toxicity has been the same as with INH—possibly because two drugs are taken rather than one. The fourth commonly studied regimen is 4 months rifampin. This has been found to have significantly better completion than 9H, with significantly less toxicity, especially hepatotoxicity. However, only one trial has evaluated efficacy and effectiveness of mono-rifampin therapy. In this trial, 3 months rifampin had somewhat better efficacy than either 3 months of isoniazid and rifampin (3HR) or 6 months isoniazid. Two large scale trials are ongoing; one is comparing efficacy and effectiveness of 9H with 4 months rifampin (both daily and self-administered), while the second, which is nearing completion, compares daily self-administered 9H with 3 months directly observed once weekly INH combined with rifapentine. The results of these two trials will likely shape future recommendations substantially.

Key words: isoniazid, latent, rifampin, prevention, tuberculosis.

INTRODUCTION

Treatment of latent tuberculosis infection (LTBI) has been a key component of TB control programmes in many high-income countries for decades, because it was first recognized that the development of disease could be prevented in guinea pigs[1] and humans.[2] Soon after isoniazid (INH) was discovered to be effective in treatment of disease, it was found to be effective in preventing disease as well. For several decades, INH was the only regimen for LTBI therapy, and, given efficacy of 90%[3] if taken properly, this remains the current standard. However, INH therapy is plagued by several problems. To maximize efficacy, the recommended duration is 9 months;[3] this substantially reduces acceptance and subsequent adherence by patients.[4,5] Toxicity can occur, which necessitates close follow up and this substantially increases costs.[6] In addition, the risk of serious toxicity, including potentially fatal hepatotoxicity, is of concern to patients and providers, resulting in significant underuse.[7]

As a result of these problems there has been considerable interest in finding shorter, safer and less costly regimens, with similar efficacy. Over the past 20 years, many studies have assessed alternative

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regimens using different drugs, individually and in combination, as well as different dosing schedules.

PERSONS WHO SHOULD BE CONSIDERED FOR LATENT TUBERCULOSIS INFECTION TESTING AND TREATMENT

Latent tuberculosis infection testing, using either the tuberculin skin test (TST) or an interferon-gamma release assay (IGRA), should be considered for persons who are at risk for *Mycobacterium tuberculosis* infection or progression to TB disease. One approach to determining which groups should be tested and treated for LTBI, modified from the Canadian Tuberculosis Standards, is shown in Table 1.[8] The USA follows the American Thoracic Society (ATS)/Centers for Disease Control and Prevention (CDC) guidelines, which are very similar, but use slightly different risk categories and do not include age criteria.[48]

The WHO recommendations for INH preventive treatment were developed for medium and high TB incidence countries and focus on HIV-infected persons and children who are household contacts of persons with infectious TB.[49] In general, it is recommended that persons who have positive TST or IGRA results receive treatment. However, the risk of not receiving LTBI treatment (i.e. the risk of developing TB disease) versus the risk of receiving treatment (i.e. the risk of adverse events) must be weighed for each individual before deciding on whether to start LTBI therapy.

ISONIAZID FOR LATENT TUBERCULOSIS INFECTION TREATMENT

Latent tuberculosis (TB) infection is defined as infection with *M. tuberculosis* as manifested by a positive TST or IGRA result, but without evidence of active TB disease including symptoms, progressive

Table 1 Risk factors for the development of active tuberculosis among persons infected with *Mycobacterium tuberculosis*

Risk factor	Estimated risk for TB relative to persons with no known risk factor	References
High risk (testing and treatment for LTBI recommended for all ages†)		
AIDS	110–170	9,10
HIV	50–110	11,12
Transplantation (related to immune-suppressant therapy)	20–74	13–16
Silicosis	30	17,18
Chronic renal failure requiring hemodialysis	10–25	19–22
Carcinoma of head and neck	16.0	23
Recent TB infection (<2 years)	15.0	24,25
Abnormal chest x-ray—with upper lobe fibronodular disease typical of healed TB infection	6–19	26–28
TNF-alpha inhibitors	1.7–9.0	29–32
Moderate risk (testing and treatment for LTBI recommended if age <65 years†)		
Treatment with glucocorticoids	4.9	33
Diabetes mellitus (all types)	2–3.6	34–37
Young age when infected (0–4 years)	2.2–5	38
Slightly increased risk (testing and treatment for LTBI recommended if age <50 years†)		
Underweight (<90% ideal body weight; for most persons, this is a BMI ≤ 20)	2–3	39
Cigarette smoker (1 pack/day)	2–3	40,41
Abnormal chest x-ray—granuloma	2	27,42
Low risk (testing and treatment for LTBI recommended if age <35 years†)		
Infected person, no known risk factor, normal chest x-ray ('low-risk reactor')	1	43
Very low risk (treatment of LTBI not usually recommended)		
Person with positive two-step (booster), no other known risk factor, and normal chest x-ray	0.5	Extrapolated from[43] and[44]

† These age and risks stratified recommendations for treatment are based upon age- specific estimates of risk of INH-induced hepatotoxicity where.
— Age >65 years, incidence >5% (from[45]).
— Age 50–65 years, hepatitis 3–5% (from[46]).
— Age 35–50 years, incidence hepatotoxicity 1–3% (from[46]).
— Age <35 years, incidence hepatotoxicity <1% (from[46,47]).
LTBI, latent tuberculosis infection; TNF, tumour necrosis factor.

radiographic changes or microbiological evidence of replicating organisms (e.g. positive culture).[48,50] INH has been the mainstay of LTBI treatment for nearly half a century. The drug was introduced as an antituberculosis medication in 1952, and was subsequently shown to be effective in preventing TB disease in an experimental guinea pig model.[1] In the 1950s and 1960s numerous controlled clinical trials demonstrating the efficacy of INH in preventing progression to TB disease were conducted in various at-risk populations in multiple locations throughout the globe.[44] With the advent of HIV, another series of studies performed in the 1990s showed that INH was also highly efficacious in preventing HIV-associated TB disease.[51] As the use of INH for LTBI treatment became more widespread, however, its limitations also became apparent. Adverse effects, most notably hepatotoxicity, can be severe, if rare, and completion rates of a 6–9-month course of therapy are generally low.[52,53] Nevertheless, INH remains the preferred medication for LTBI therapy. In the USA, for example, it is estimated that of the 300 000–400 000 persons who start LTBI treatment each year, more than 90% take INH.[48,54]

Placebo-controlled trials of isoniazid therapy for latent tuberculosis infection

The ability of INH to prevent reactivation of TB was first demonstrated in the 1950s. A series of controlled trials were conducted by the United States Public Health Service (USPHS) in a number of populations including household contacts of TB patients, residents of mental health facilities and native Alaskans (Table 2).[44] In two USPHS studies conducted in household contacts, the contacts of a TB patient, regardless of their TST result, were randomly assigned to receive 12 months of daily INH or placebo by household.[55,56] The two studies enrolled a total of nearly 14 000 patients per arm; participants were followed for up to 10 years. In total, 215 new cases of TB developed in the placebo-treated group, compared with 86 TB cases in the INH group. Overall, this translated into new TB case rates of 15.4 per 1000 contacts enrolled in the placebo arm and 6.2 per 1000 contacts enrolled in the INH arm, that is a 60% reduction with INH.[44,55,56] Among persons with a reactive TST, the new TB rates were 26.9 per 1000 and 11.1 per 1000 in the placebo and INH groups, respectively, translating into a 59% reduction with INH. In the late 1950s and early 1960s, smaller controlled trials performed by other investigators in the Netherlands, Kenya and the Philippines found the INH treatment decreased the number of new TB cases among contacts of TB patients by as much as 92%.[44,62–64]

Between 1957 and 1960, the USPHS randomized approximately 25 000 residents of 37 chronic mental health facilities by ward to receive 12 months of INH or placebo.[44,57] As with the USPHS household contact trials, this trial also included TST reactors and nonreactors. Over a 10-year observation period the new TB case rate was 62% less in the INH group compared with the placebo group for all randomized subjects. There was a 68% reduction in new TB case rates with INH in persons with a TST result of 10 mm or greater.

A community-based study was conducted among native Alaskans (Eskimos) living in the Bethel Hospital service area of south-western Alaska beginning in 1957.[58] Households in 28 villages were randomly assigned to receive 12 months of INH versus placebo. More than 3000 patients were evaluated in each arm with a median observation time of 69 months. The percentage of TB cases in the INH arm was less than half of that in the placebo arm (1.90 vs 4.67). Skin testing was only performed in 845 patients in each group, but INH appeared to have an even greater effect in persons with a TST result of at least 5 mm. Among those with a TST result of at least 5 mm, the percentage of new TB cases was 5.6 in subjects given the placebo, but 0.6 in subjects given INH (90% reduction). In a follow-up paper, it was shown that the protective effect of INH persisted through the final evaluation 19 years after the study began.[65]

Clinical trials in persons at high risk for progression to tuberculosis disease: Inactive tuberculosis, silicosis and treatment with tumour necrosis factor-alpha antagonists

A number of studies have examined the efficacy of INH in preventing reactivation of TB disease in persons with inactive TB. In general, inactive TB was defined by the presence of stable fibrotic or fibronodular lesions on chest radiograph without other evidence of disease activity such as a positive sputum culture. However, these studies differed somewhat in their inclusion criteria, particularly as to whether they allowed enrolment of persons who received previous treatment for TB disease that often had included INH. A USPHS trial was performed in 27 health departments and allowed for enrolment of persons with inactive TB chest radiograph lesions with or without a prior known history of active disease.[44] This study included patients regardless of whether they received prior treatment for TB disease. The only category of subjects for whom there was a substantial reduction in subsequent active TB with INH was in those without any known previous history of active TB. In this category, the arm that received INH for 12 months had a 63% lower rate of new active TB compared with placebo. Similarly, a US Veterans Administration study of more than 7000 patients with inactive TB found that 12–24 months of INH decreased TB reactivation by 60% compared with placebo only in patients who had not been treated previously for TB disease.[66]

Two clinical trials of INH in persons with inactive TB limited enrollees to those who had no or inadequate (<90 days) TB disease therapy and also examined the efficacy of shorter durations of INH treatment.[59,67,68] A Canadian clinical trial assigned subjects to two treatment arms, INH or a combination of INH and para-aminosalicylic acid, versus a control arm (no drug, placebo or refused treatment). Medication was given for up to 18 months, but the analysis examined the effect of at least 6 months of

Table 2 Placebo controlled studies of INH efficacy for the treatment of LTBI

Authors (references)	Years	Location	Population	Duration of INH (months)	Reduction in TB rates
Ferebee[44]; Mount and Ferebee[55]	1956–1957	USA, multiple sites	Household contacts	12	68% reduction in first 15 months of follow up; 60% reduction after 10 years[†]
Ferebee[44]; Ferebee and Mount[56]	1957–1960	USA, multiple sites	Household contacts	12	76% reduction in first 15 months; 60% reduction after 10 years[†]
Ferebee[44]; Ferebee *et al*.[57]	1957–1960	USA, multiple sites	Residents of mental institutions	12	88% reduction in first 15 months; 62% reduction after 10 years
Comstock *et al*.[58]	1957–1964	Alaska	Native Alaskans	12	59% reduction after 43–76 months
International Union Against Tuberculosis Committee on Prophylaxis[59]	Started 1969	Eastern Europe	Person with fibrotic pulmonary lesions (inactive TB)	3, 6, 12	After 5 years follow up in all randomized 21% reduction for 3 months INH 65% reduction for 6 months INH 75% reduction for 12 months INH After 5 years follow up in completer/compliers 30% reduction for 3 months INH 69% reduction for 6 months INH 93% reduction for 12 months INH
Pape *et al*.[60]	1983–1989	Haiti	HIV-infected persons	12	71% reduction after 60 months
Whalen *et al*.[61]	1993–1995	Uganda	HIV-infected persons	6	For TST-positive persons; 67% reduction after 15 months In anergic persons: No reduction

[†] 60% reduction for 10 year follow up was calculated from aggregate results of first two studies listed (references[8] and[48]) as reported in reference.[2]
INH, isoniazid; TB, tuberculosis; TST, tuberculin skin test.

therapy.[67,68] In the initial analysis when most patients had at least 3 years of participation in the trial, the reactivation rate in the control arm was 4.9 per 1000 per year, which was comparable to the reactivation rate in subjects who took less than 6 months of INH (5.1 per 1000 per year), but almost 4 times as high as those who took at least 6 months of INH (1.3 per 1000 per year). The longer-term analysis done when controls had an average of 8.5 years of enrolment had similar findings in terms of reactivation rates: controls—3.9 per 1000 per year, less than 6 months of INH—3.9 per 1000 per year, and at least 6 months of INH—1.2 per 1000 per year. The International Union Against Tuberculosis (IUAT) conducted a controlled trial in Eastern Europe of multiple durations of INH for patients with inactive TB and no history of prior TB treatment.[59] Nearly 28 000 patients with fibrotic lesions on chest radiograph were randomized to receive placebo or 12, 24 or 52 weeks of INH. The patients were anticipated to be followed for 5 years from study entry and the primary outcome of interest was culture positive TB per 1000 persons at risk. Compared with placebo, the reduction in TB rates was 21% for 12 weeks of INH, 65% for 24 weeks of INH and 75% for 52 weeks of INH.

Persons with the occupational lung disease silicosis are at substantially increased risk of progressing to TB disease if infected with *M. tuberculosis*. In Hong Kong, a 24-week INH regimen was evaluated as part of a randomized placebo-controlled trial that also examined short-course rifampin and combination INH/rifampin regimens for the prevention of TB disease in patients with silicosis.[17] Enrolled subjects were followed for up to 60 months. The cumulative percentage of patients who developed TB disease over 60 months was almost twice as high in the placebo arm (27%) compared with the INH arm (14%).

There are a number of clinical conditions that result in increased risk of progression from LTBI to TB disease (Table 1). Other than for persons with recent infection (e.g. contacts), fibrotic abnormalities on chest radiograph, silicosis (all three described above) and HIV (described below), clinical trials of the efficacy of INH (or other regimens) for the treatment of LTBI have not been conducted in specific high-risk groups. For patients with rheumatoid arthritis receiving tumour necrosis factor-alpha antagonists, a registry-based study in Spain found that rates of TB disease were reduced by 78% following the introduction of new recommendations for the management of LTBI.[29] The recommendations included LTBI treatment with INH for 9 months for those patients receiving tumour necrosis factor-alpha antagonists with a TST result of at least 5 mm induration. Even in the absence of clinical trials specific to most of the high-risk groups, LTBI treatment with INH is generally recommended for persons in these groups that have positive TST results.[8,48]

Duration of isoniazid treatment

By the 1980s, multiple placebo-controlled clinical trials established the efficacy of INH in preventing TB disease in multiple populations at risk for TB. Most of the studies examined only one duration of INH, 12 months, which became the initial standard. Some later studies evaluated shorter regimens, and the data suggested a 6-month regimen was also efficacious.[17,59] Only one of these trials, however, involved a direct comparison between the 6- and 12-month regimens.[59]

Another approach for attempting to determine the minimum effective duration of INH was based on examining the amount of medication actually taken by patients who were enrolled in the 12-month INH trials. The authors of the initial report of the Bethel Alaska trial noted that patients who took as little as 40–59% of the intended 12 months of INH had the same rate of subsequent TB disease as those who took 80–100% of prescribed medication.[58] This led them to conclude that 6 months of medication might be adequate. Although patients took medication for as long as 18 months in a Canadian study of INH treatment in persons with inactive TB, the investigators found that at least 6 months of treatment was effective in preventing reactivation of TB.[67,68]

In 1986, Snider *et al*. published a cost-effectiveness analysis of various durations of INH using data from the IUAT trial in Eastern Europe.[59,69] The evaluation found that the 6-month regimen was most cost-effective, costing $7112 per TB case prevented. Each additional case prevented using the 12-month regimen was estimated to cost $80 807.[69] This analysis was highly influential in the USA, with many public health programmes adopting the 6-month INH regimen for treatment of persons with LTBI and normal chest radiographs in the 1980s and 1990s.[48,70]

In 1999, Comstock re-evaluated data from multiple studies to determine the optimal duration of INH therapy for LTBI[3]. In looking at the Eastern European IUAT trial data, he noted that while the difference in reduction in the 5-year incidence of TB between the 6- and 12-month regimens was modest (65% vs 75%) when analysed by regimen assignment (i.e. intent to treat), the difference was much greater when the analysis was limited to enrollees labelled as 'completer–compliers' (took at least 80% of doses for the intended duration).[59] In this subgroup reduction in TB was 69% for persons in the 6-month arm versus 93% in the 12-month arm. Therefore, the true efficacy of the 12-month regimen was superior, and the nearly equivalent effectiveness was a result of poorer adherence to the 12-month regimen. Comstock found no benefit to extending INH treatment beyond 12 months based on data from the Veterans Administration study and his own Bethel Alaska study, both of which showed no additional reduction in TB disease with a 24-month regimen compared with a 12-month regimen.[65,66] Based on these studies he concluded that 6 months of INH was inadequate, but more than 12 months was unnecessary.

Comstock refined the optimal duration of INH therapy by further examining the findings from one of the USPHS household contact studies and the Bethel Alaska study (Fig. 1).[3] In the USPHS household contact study, it was observed that if patients took at least 80% of their medication for at least 10 months, the reduction in TB was 68% compared with only 16%

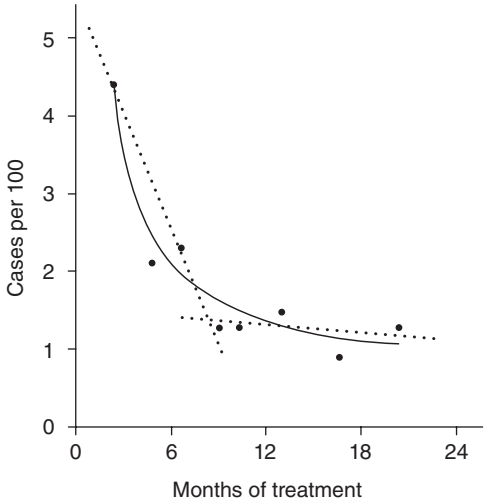

Figure 1 How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? (from Comstock, [3] Int J Tuberc Lung Dis. 1999; 3:847–50). Tuberculosis case rates (%) in the Bethel Isoniazid Studies population according to the number of months isoniazid was taken in the combined programmes. Dots represent observed values; thin line, the calculated curve ($y = a + b/x$); and dotted lines, the calculated values based on the first four and last five observations ($y = a + bx$).

in patients who took at least 80% of their medication for less than 10 months.[44] Comstock also plotted the TB case rate in the Bethel Alaska study versus months of treatment taken and found that the decline in case rate became nearly horizontal at 9–10 months. Thus, he concluded that 9–10 months of INH was the optimal duration. The revised (and current) recommendation that 9 months of INH is the preferred duration of treatment in the USA is largely based on Comstock's analysis.[48] Therefore, while 6 months INH may appear a better option from the perspective of public health programmes who consider cost-effectiveness, clearly 9 months is the superior option from the patient's perspective—which should be the perspective adopted by individual providers caring for patients.

More recently, Smieja *et al*. published a systematic review of the ability of INH to prevent TB disease in non-HIV-infected persons.[62] The review included 11 studies (most of which have been described above) with more than 73 000 patients. The risk ratio (RR) of developing TB disease over a period of at least 2 years in persons treated with INH was 0.40 (95% CI: 0.31–0.52). However, the authors found no significant difference in the relative risk for TB when comparing persons treated for 12 months (RR 0.38, 95% CI: 02.8–0.50) to those treated for 6 months (RR 0.44, 95% CI: 0.27–0.73).

All of the studies cited above used daily dosing of INH. Current US recommendations for LTBI treatment allow for twice weekly dosing of INH when administered as directly observed preventive therapy (DOPT).[48] However, the recommendation for the use of twice weekly INH is based on the extrapolation of its efficacy in the continuation of phase of treatment of TB disease as there are no comparative studies of daily versus intermittent INH in the treatment of LTBI in HIV-uninfected persons.[48] Hence twice weekly DOPT must be considered to have a weak evidence base.

Trials of isoniazid in HIV-infected persons

For over two decades, it has been known that co-infection with HIV confers a very high risk for progression to TB disease in persons with LTBI.[11] Beginning in the late 1980s, several studies were conducted to determine the efficacy of INH for preventing TB disease in HIV-infected persons. In Haiti, 118 subjects were randomly assigned to receive INH and vitamin B6 or vitamin B6 alone for 12 months.[60] The incidence of TB disease was significantly lower in the group who received INH (2.2 per 100 person-years) compared with the group who received vitamin B6 alone (7.5 per 100 person-years). When the analysis was stratified by TST result, it was found that the odds ratio for developing TB for those who did not receive INH was 5.7 (95% CI: 1.2–29.8) for persons with a positive TST result, but 1.68 (95% CI: 0.32–8.88) for persons with negative TST results. In a trial performed in Uganda, approximately 2700 HIV-infected persons were enrolled and randomized to four regimens: placebo, INH daily for 6 months, INH and rifampin daily for 3 months, or INH, rifampin and pyrazinamide for 3 months.[61] The analysis was stratified by TST result. For subjects with a positive TST result, the relative risk for developing TB disease was 0.33 (95% CI: 0.14–0.77) in those taking INH compared with those taking placebo. In subjects with negative TST results, INH was not found to have a protective effect.

In contrast to the studies in Haiti and Uganda, a clinical trial performed in Kenya did not find a statistically significant protective effect for INH, even when limited to persons with a positive TST result.[71] In the Kenya study, approximately 685 persons were randomized to receive INH for 6 months or placebo. The adjusted rate ratio for development of TB disease in enrollees with a positive TST result for INH versus placebo was 0.6 (95% CI: 0.23–1.60). However, as noted by the investigators, only 22–23% of patients in each arm of the study were TST positive. Therefore, the power to detect a statistical difference between the treatment arms in the TST-positive subgroup was low, given that there were only 67–69 subjects per arm in this subgroup.

A twice weekly INH regimen was evaluated in a clinical trial in Zambia.[72] In this study, slightly more than 1000 patients were randomly assigned to receive twice weekly INH for 6 months, or twice weekly rifampin and pyrazinamide for 3 months or placebo. For all subjects the rate ratio for developing TB disease for INH versus placebo was 0.56, which was not statistically significant (95% CI: 0.30–1.05, $P = 0.65$). When the subgroup with a positive TST was analysed, the INH and rifampin/pyrazinamide groups were combined (i.e. any therapy vs placebo).

The TB incidence rate in this subgroup was statistically significantly lower in the combined treatment arm (2.5 per 100 person-years) compared with placebo (9.2 per 100 person-years) with a rate ratio of 0.27 (95% CI: 0.08–0.87) for treatment versus placebo. Obviously, however, with this combined analysis approach it is not possible to determine the efficacy of the twice weekly INH arm for persons with a positive TST result.

A systematic review of the use of various regimens for the prevention of TB disease in HIV-infected persons examined 11 trials with more than 8000 participants.[51] For the overall population, which included TST-negative and TST-positive subjects, the relative risk for developing TB disease for patients treated with INH compared with placebo was 0.67 (95% CI: 0.51–0.87). The relative risk for developing TB disease for persons with a positive TST result was 0.38 (95% CI: 0.25–0.57), but this risk was not stratified by LTBI treatment regimen so it is not possible to determine the level of protection provided by INH specifically. For persons who had negative TST results or with confirmed anergy, the risk reduction was less and not statistically significant.

While there is good evidence that INH therapy can prevent tuberculosis in HIV-infected persons with LTBI, the optimal duration of treatment is less clear. It appears that both the 6- and 12-month INH regimens are efficacious, but no trials have assessed the optimal duration of INH by directly comparing regimens of different duration of INH in HIV-infected populations. In the absence of such trials (which frankly seem unlikely to be conducted), it would seem prudent to extrapolate from evidence in non-HIV-infected populations that 9 months of INH is the optimal duration of therapy in HIV-infected persons.[48] The duration of protection of INH treatment in HIV-infected persons is uncertain. One of the concerns is the potential for re-infection after completion of LTBI treatment, especially in high TB burden settings. Longer-term follow-up studies suggest the benefit of INH in high TB burden settings diminishes over time and appears to be lost by 2.5–3.0 years.[73,74]

Adverse events with isoniazid

Adverse effects caused by INH pose one of the limitations to its effectiveness, especially when it is used to treat LTBI, which is an asymptomatic condition (Table 3). The most well-known and concerning adverse effect is hepatotoxicity. Although there were several reports of jaundice occurring in the USPHS clinical trials conducted in the 1950s and 1960s, these were not definitively linked to INH.[44] Following the enthusiastic endorsement by the ATS of INH therapy to prevent active TB,[79] INH was used much more widely. Soon after, INH was found to cause asymptomatic transaminase elevation and frank liver injury.[80] The potential for INH-induced hepatotoxicity received greater attention in relation to a TB outbreak in the Capitol Hill area of Washington, DC in 1970.[76] Nineteen of 2321 contacts of TB patients treated with INH developed hepatotoxicity, which resulted in two deaths. There were no cases of hepatotoxicity in a matched control group. This incident prompted the USPHS to undertake a large surveillance study of INH-associated liver injury.[46] Nearly 14 000 persons taking INH were enrolled at 21 health departments across the USA. One hundred seventy-four (1.3% of persons enrolled) probable and possible cases of INH hepatotoxicity were identified, including eight deaths. Factors associated with INH hepatotoxicity were age (>35 years old) and daily alcohol consumption.

A meta-analysis of six studies (including the Capitol Hill investigation, the USPHS surveillance study and the Eastern European IUAT trial) that had a combined total of more than 38 000 persons treated with INH found that overall 0.6% developed hepatotoxicity.[81] The percentage of persons with hepatotoxicity varied by study from 0 to 2.9%. However, more recent observational studies suggest that the occurrence of INH hepatotoxicity can be substantially lower when routine clinical monitoring for adverse effects is used. Public health clinics in Seattle (approximately 11 000 patients) and San Diego (approximately 3800 patients) reported incidences of INH-associated hepatotoxicity of 0.1% and 0.3%, respectively, with no deaths and only one hospitalization.[77,78]

Peripheral neuropathy, related to the inhibitory effect of INH on the function of pyridoxine metabolites, is another well-recognized adverse effect. Peripheral neuropathy is unusual in otherwise healthy individuals (<0.2%), and is more commonly seen in chronic alcoholics, malnourished persons and pregnant women.[52,70,82] INH-associated peripheral neuropathy can be both prevented and treated by concurrent administration of pyridoxine (vitamin B6).

Other rare adverse effects that have been attributed to INH include anaemia, leucopenia, seizures and a systemic lupus erythematosus-like syndrome.[52,82,83] With regard to the latter, it is more common to see asymptomatic elevations in antinuclear antibody (ANA) titres than the actual lupus-like syndrome. Non-specific adverse effects seen with most medications, such as rash, nausea and fatigue, are seen more frequently.[83]

Compliance and completion of isoniazid

While the controlled trials demonstrated that INH was efficacious for the treatment of LTBI, the effectiveness of this intervention is dependent upon physicians prescribing, as well as patients accepting and completing a full course of medication. To begin with, physicians may not recommend therapy, even when it appears indicated,[84,85] particularly in older patients.[7] In several large-scale studies physicians did not recommend LTBI therapy to 20–30% of patients who appeared eligible.[84–89] Subsequently, a substantial portion of patients may decline LTBI treatment when it is offered. In a retrospective study of clinics providing LTBI treatment, 123 (17.1%) of 720 patients did not accept treatment when eligible.[90] A study of 259 health-care workers who were eligible for and offered an appointment to begin LTBI treatment found that 80 (30.9%) either did not attend the appointment or

Table 3 Adverse events, particularly hepatotoxicity, in studies of INH treatment of LTBI (placebo-controlled trials, or observational studies)

Authors (references)	Years	Type of study	Regimens	Rate of adverse events	Rate of hepatotoxicity	Other significant findings
Placebo-controlled randomized trials						
Ferebee[44]; Mount and Ferebee[55]; Ferebee and Mount[56]	1957–1960	Two randomized clinical trials in household contacts	1) INH (12 months)	1.9% for INH	Not mentioned	60% of adverse events categorized as gastrointestinal
			2) Placebo	1.5% for placebo		
Riska[75]	Started 1969	Randomized clinical trial in persons with fibrotic pulmonary lesions (inactive TB)	1) INH (multiple durations compared)	N/A	95/20 838 (0.5%) for INH	
			2) Placebo		7/6991 (0.1%) for placebo	
Hawken *et al.*[71]	1992–1994	Randomized clinical trial in HIV-infected persons	1) INH (6 months)	4.75 per 100 person-years in INH arm	18/342 (5.3%) in INH arm	
			2) Placebo	3.37 per 100 person-years in placebo arm	12/342 (3.5%) in placebo arm	
Observational studies						
Garibaldi *et al.*[76]	1970	Observational cohort in setting of TB outbreak	INH	N/A	19/2321 (0.8%)	2 deaths
Kopanoff *et al.*[46]	1971–1972	Surveillance of public health departments	INH	N/A	92/13 838 (1.04%)[†] probable cases	8 deaths, rate of hepatotoxicity increased with older age and daily alcohol consumption
Nolan *et al.*[77]	1989–1995	Observational cohort of persons with LTBI in public health clinic	INH	N/A	11/11 141 (0.1%)	No deaths, 1 hospitalization, rate of hepatotoxicity increased with older age
LoBue and Moser[78]	1999–2002	Observational cohort of persons with LTBI in public health clinic	INH (6–9 months)	18%, but only 1.4% stopped treatment because of adverse event	10/3788 (0.3%)	No deaths, no hospitalizations, rate of adverse effects increased with older age

[†] Rate adjusted for length of time under observation.
INH, isoniazid; LTBI, latent tuberculosis infection; TB, tuberculosis.

did not agree to take INH.[91] In a US cohort of more than 40 000 contacts to sputum smear positive TB cases, only 72% started LTBI treatment.[86] With regard to completion, a systematic review of 78 studies of LTBI treatment adherence found that treatment completion rates varied from 19% to 96%.[53] However, these studies were quite heterogeneous and some included non-INH regimens. If one restricts the analysis to the largest (at least 3000 patients) studies that used INH only, the completion rates are much more consistent at 61–64%.[53,77,78,86,92,93]

There are several obstacles to acceptance and completion of INH therapy. There is a vast literature on adherence with medications; reviews suggest that adherence is lower with regimens that are longer, more complex, and for asymptomatic conditions. In addition patients' perceptions of risk of disease, and of the benefits and risks of therapy will affect adherence.[4] As has already been discussed, INH has a number of adverse effects, the medication is being taken for an asymptomatic condition that has a relatively small chance of progressing to illness and the course of treatment is long (at least 6 months). In addition there are very substantial differences in LTBI completion rates reported by different centres; these differences have never been fully explored, nor explained. The high completion rates reported by some centres, such as the San Francisco programme,[94] suggest that these 'clinic factors' are very important, and the between-centre differences that contribute to the differences in completion rates are worthy of further investigation. Most sociodemographic characteristics, such as age, gender, education or occupation, are inconsistently associated with adherence.[4,5] However, certain patient factors such as homelessness and substance abuse have been associated with poor adherence to treatment for TB disease.[53,78,95] Several interventions have been attempted to improve adherence, such as employment of DOPT, enhanced patient education, incentives and peer advisors.[53] These interventions have met with mixed success with DOPT providing the most consistent improvement in completion rates.[53,96–101]

Cost considerations of isoniazid therapy

In economic analyses, INH treatment for LTBI has been found consistently to be a cost-effective intervention, and in the majority of scenarios a cost-saving intervention (Table 4). Cost savings are likely to be greater in populations that are younger, and/or at greater risk to progress from LTBI to TB disease. For example Rose *et al*. in their 1988 analysis found that INH therapy cost $12 625 per year of life gained and $35 011 per death averted for persons at low risk for progression to TB disease. However, they found that INH therapy was cost-saving for persons at high risk for progression, such as young adults with TST conversion.[102] Multiple other studies and modelling analyses have shown that relative to no treatment, INH treatment for LTBI will be cost-saving in populations such as young adults with positive TST results, patients with inactive TB, close contacts of patients with TB disease and inmates of correctional facilities.[6,94,104,106–108] As previously discussed, because of the difference in completion rates, Snider *et al*. found that 6 months of INH treatment was more cost-effective than 12 months.[69] However, no study has compared 6 months to the current standard of 9 months INH. In HIV-infected persons, both the 6- and 12-month INH regimens were found to be cost-saving compared with no treatment.[103]

Current recommendations for isoniazid

Isoniazid daily for 9 months is the preferred therapy for LTBI in recommendations of the ATS and the CDC.[48] The daily 9-month regimen is recommended for all groups including HIV-infected persons, children and persons with inactive TB. Twice weekly INH for 9 months administered as DOT is an acceptable alternative for all groups. INH for 6 months, either daily or twice weekly (the later given as DOT), are acceptable alternatives for adults who are not HIV-infected. Guidelines for use of INH to treat LTBI provided in the Canadian Tuberculosis Standards are essentially the same.[8] However, in the UK, the National Institute for Health and Clinical Excellence guidelines recommend a 6-month duration of INH for all groups including children and HIV-infected persons.[109] The World Health Organization also recommends 6 months of INH for LTBI, generally limited to HIV-infected persons and young children in households of patients with infectious pulmonary TB.[49]

As discussed in the section on adverse effects of INH, peripheral neuropathy caused by interference with metabolism of pyridoxine is uncommon at the recommended dose of INH. Therefore, routine use of pyridoxine with INH is not necessary. However, in persons with conditions in which neuropathy is common or dietary pyridoxine intake may be low (e.g. diabetes, uraemia, alcoholism, malnutrition, pregnancy and HIV infection), pyridoxine should be given with INH[48].

ALTERNATIVE REGIMENS FOR LATENT TUBERCULOSIS INFECTION

The problems with INH discussed above have resulted in considerable interest in finding shorter, safer, yet equally effective therapy for LTBI. This interest has spurred multiple randomized trials and observational studies investigating the acceptability, safety and effectiveness of several alternative regimens for treatment of LTBI. Early experiments in a mouse model, summarized in Figure 2, demonstrated the potential efficacy of three short-course regimens that included rifampin, with or without companion medications.[110] This study prompted a number of clinical investigations of these three regimens:

- 2 months rifampin-pyrazinamide (2RZ)
- 3–4 months INH-rifampin (A few studies have investigated 3 months INH- rifapentine taken once weekly)
- 4 months rifampin alone (4R)

Table 4 Selected LTBI cost and cost-effectiveness studies

Authors (reference, baseline year(s) of cost analysis)	Group treated (actual or hypothetical)	Regimens	Assumed reduction in TB	Assumed medication cost	Assumed total treatment cost[†]	Main findings of study
Snider *et al.*[69], 1983)	Fibrotic lesions on chest radiograph consistent with prior TB	INH for 12 weeks	21%	$2.70	$63.97	24-week regimen was most cost-effective, costing $7112 per TB case prevented. Each additional case prevented using the 12-month regimen was estimated to cost $80 807.
		INH for 24 weeks	65%	$5.40	$124.80	
		INH for 52 weeks	75%	$10.80	$248.09	
Rose *et al.* [102], 1984–1985)	White male TST reactors 55 years old and white male TST converters 20 years old	INH for 12 months	70%	$38.00[‡]	$148.00–$226.00	LTBI treatment of high-risk TST converters was cost-saving. Treatment of lower-risk TST reactors was still cost-effective ($12 625 per year of life gained and $35 011 to avert 1 death).
Rose [103], 1997)[§]	HIV-infected with CD4 count <200 cells/mm^3 and positive TST	INH for 6 months	83%	Not provided	$190.00 SAT $875.00 DOPT	All regimens except INH + RIF + PZA increased life expectancy 6.2–8.7 months) and were cost-saving (1–7 dollars saved for each dollar spent).
		INH for 12 months	67–75%	Not provided	$361.00	
		INH + RIF for 3 months	60%	Not provided	$456.00	
		RIF + PZA for 2 months	73–82%	Not provided	$465.00 SAT $468.00 DOPT	
		INH + RIF + PZA for 3 months	49%	Not provided	$889.00	
Jasmer *et al.* [94], 1999)	Previous radiographic evidence of TB	INH for 12 months	79.8%	$11.00	$619.00	Both regimens increased life expectancy 1.4–1.5 years. Compared with 12-months INH, 4 months INH + RIF produced a net incremental savings of $135 per patient.
		INH + RIF for 4 months	83.6%	$138.00	$608.00	
Jasmer *et al.* [104], 2002)	Adults with HIV and LTBI	INH for 6 months	69%	$14.00	$347.00	Both regimens increase life expectancy by 1.2 years, but RIF + PZA costs $273 more per patient started.
		RIF + PZA for 2 months	69%	$184.00	$640.00	
Menzies *et al.* [105], 2004)	Adults with a positive TST	INH for 9 months	Not applicable	2.07[¶]	497.00	RIF had better completion rates and lower costs and adverse effects than INH.
		RIF for 4 months	Not applicable	10.48	309.00	
Diel *et al.* [106], 2005)	TB patient contacts with LTBI either 20 years old or 40 years old	INH 9–12 months	80%	70.2[††]	201.5	INH LTBI treatment resulted in an annual savings of 18 742–20 862 euros per 1000 contacts treated.
Holland *et al.* [107], 2009)	Persons with LTBI	INH for 9 months	93%[‡‡]	$5.40	$237.33 SAT $1841.04 DOPT	All regimens were dominated by RIF, except INH + RPT, which was more effective at a cost of $48 997 per QALY. Compared with INH, INH + RPT was more effective at a cost of $25 207 per QALY.
		RIF for 4 months	93%	$55.20	$212.28	
		INH + RPT once weekly for 3 months	93%	$28.56	$503.46 DOPT	

[†] Usually includes cost of medication, clinic visits and laboratory tests.
[‡] Includes cost of vitamin B6.
[§] Estimates for HIV-infected patients only.
[¶] Costs for this study are in Canadian dollars.
[††] Costs for this study are in euros.
[‡‡] TB reduction estimates in this study are based treatment being completed. The overall model accounted for differences in completion rates.

B6, Vitamin B6; CD4, ••; DOPT, directly observed preventive therapy (twice weekly unless otherwise specified); INH, isoniazid; PZA, pyrazinamide; QALY, quality-adjusted life-year; RIF, rifampin; RPT, rifapentine; SAT, self-administered therapy (always daily); TB, tuberculosis; TST, tuberculin skin test.

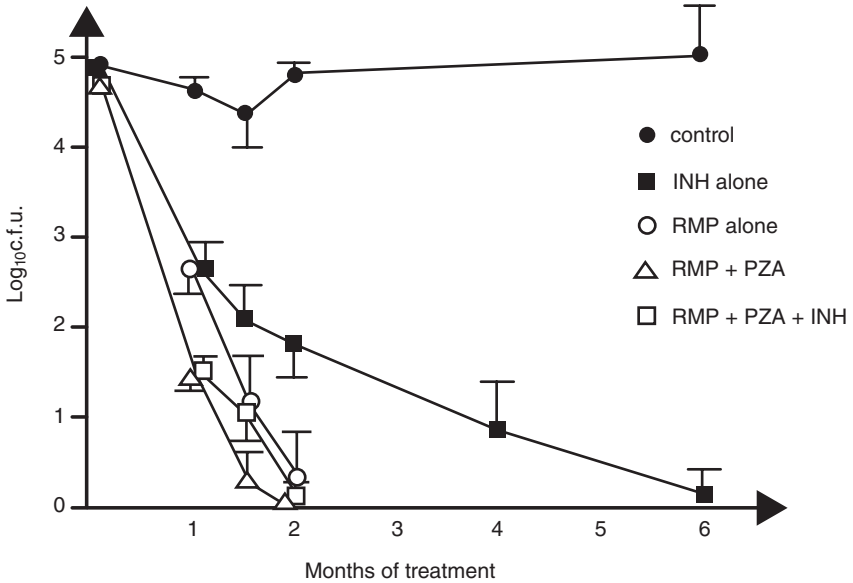

Figure 2 Experimental study of short-course preventive therapy in mice (from Lecoeur *et al.*,[110] Am Rev Respir Dis 1989:140:1189–1193). INH, Isoniazid; PZA, pyrazinamide; RMP, rifampin.

2 months Rifampin-Pyrazinamide

The randomized trials, and selected observational studies that compared 2RZ with placebo, and/or 6 months INH (in one study, 12 months INH was the standard arm[111]) are summarized in Table 5. Most of the earliest trials were conducted among HIV-infected persons;[72,111–114] in all these studies the efficacy of 2RZ was equivalent to that of the INH arm—if not somewhat better. In most trials serious adverse events were somewhat more frequent in subjects taking 2RZ than those taking INH, although hepatotoxicity was not different. Interestingly, despite the much shorter duration of therapy, completion of 2RZ therapy was significantly better than completion of INH, in only two of these trials.[111,112]

Results in non-HIV-infected subjects were radically different (Table 5).[115–118,121,122] Unfortunately, most of these studies were available only after 2000, the year when new US recommendations were published strongly endorsing use of 2RZ[48]. Following publication of these recommendations, use of 2RZ was enthusiastically adopted in many jurisdictions. Widespread adoption of the 2RZ regimen was soon followed by widespread reports of severe liver toxicity,[123–125] with fatalities,[126] or requiring liver transplantation.[127] Subsequently published studies revealed a consistently higher rate of hepatotoxicity among non-HIV-infected persons taking the 2RZ regimen.[115–118,121,122] Case reports indicated that severe liver injury could happen at the end of therapy,[125] and despite monitoring liver transaminases every 2 weeks.[125] As a result, recommendations for use of this regimen were revised[128] that this regimen should be used with very careful follow up including biweekly transaminase monitoring, and only in situations where treatment regimens of 3–4 months are not feasible. This regimen has been largely abandoned, although its use appears to be safe in children,[119] and in HIV-infected persons.

3–4 months isoniazid-rifampin

Results of trials and observational studies that have evaluated the combination of INH and rifampin given for 3–4 months are shown in Table 6.[17,61,94,113,115,129–133] Interestingly, in almost all studies the rate of completion was not better than with 6 months of INH (even when compared with 12 months INH in a report from San Francisco[94]). In one observational study among aboriginals in Saskatchewan, Canada, 19% completed 12 months of daily, self-administered INH, compared with 80% completion of 6 months twice weekly combined INH-rifampin that was given under direct observation (i.e. as DOPT).[133]

Serious adverse events have been very similar in studies, except one relatively small study of HIV-infected persons in Spain, where the rate was very substantially higher with 6 months INH.[130]

In the randomized trials the protective effectiveness of 3–4 months INH and rifampin has been similar to that of 6 months INH,[135] although it was significantly higher in the non-randomized Saskatchewan study, likely reflecting the large difference in completion rates.

One trial comparing 6 months daily self-administered INH and 3 months once weekly INH-rifapentine (3HRpt) in HIV-infected persons has been published.[134] In this trial, very few persons developed active TB, so rates of TB were low. The rate was slightly, but not significantly higher in the group randomized to the 3HRpt arm. A large-scale trial comparing 3HRpt with 9 months daily self-administered INH (9H) is nearing completion; results are expected in 2012.

4 months rifampin

One of the alternative regimens recommended in 2000 by the ATS[48] (and later also by the Canadian

Table 5 Treatment completion, serious adverse events and rates of TB in studies comparing 6 months Isoniazid (6H) to 2 months rifampin and pyrazinamide (2RZ)

	Study population					Completing therapy (%)		Serious adverse events (%)		Rates of active TB (cumulative %)	
				Number[†]							
Author (reference)	Country	Age (years, mean or range)	HIV (%)	6H	2RZ	6H	2RZ	6H	2RZ	6H	2RZ
Randomized trials											
Halsey *et al.*[‡112]	Haiti	31	100%	392	392	52%	72%	0	0	3.8%	5.8%
Mwinga *et al.*[§72]	Zambia	31	100%	360	360	66%	75%	3.3%	3.9%	7.5%	6.9%
Gordin *et al.*[¶111]	Internat'l	37	100%	791	792	69%	80%	6.1%	9.5%	3.7%	3.5%
Rivero[113]	Spain	32	100%	107	101	64%	62%	6.5%	12%	3.7%	2.0%
Rivero *et al.*[††114]	Spain	32	100%	83	77	78%	80%	7.2%	16.9%	3.6%	1.3%
Geiter[115]	USA, Canada	18–65	0	132	139	63%	68%	1.5%	5.8%	nr	nr
Jasmer *et al.*[116]	USA	37	0	64	69	57%	61%	3%	9%	nr	nr
Leung *et al.*[117]	Hong Kong	60	0	36	40	64%	55	3%[‡‡]	35%[‡‡]	nr	nr
Tortajada *et al.*[118]	Spain	nr	0	199	153	63%	47%	2.5%	9.8%	nr	nr
Graczk *et al.*[119]	Poland	18–65	0	88	106	68%	91%	0	2.9%	0	0
Non-Randomized studies											
Narita *et al.*[120]	USA	40	100%	118	135	63%	93%	0	3.7%	nr	nr
MacNeill *et al.*[121]	USA	37	1.5%	114	110	59%	71%	4%	13%	nr	nr
Van Hest *et al.*[122]	Holland	25	0.2%	528	166	nr	nr	3.4%	8.4%	nr	nr

[†] Number of subjects starting therapy in the isoniazid or rifampin-pyrazinamide arms ONLY.
[‡] Halsey study—Therapy in both arms given twice weekly.
[§] Mwinga study: 3 months rifampin-pyrazinamide given.
[¶] Gordin study: 12 months isoniazid given.
[††] Rivero study (2nd): Randomized controlled trial (RCT) in HIV-infected with negative tuberculin skin test and anergy.
[‡‡] Leung study: Only serious adverse event (SAE) of Grade 3–4 hepatotoxicity shown.
nr, not reported; TB, tuberculosis.

Table 6 Treatment completion, serious adverse events and rates of TB in studies comparing 6 months isoniazid (6H) to 3–4 months of isoniazid and rifampin (3–4HR) (all regimens daily and self-administered unless otherwise)

	Study population					Completing therapy (%)		Serious adverse events (%)		Rates of active TB (cumulative %)	
				Number[†]							
Author (reference)	Country	Age (years, mean or range)	HIV (%)	6H	3–4HR	6H	3–4HR	6H	3–4HR	6H	3–4HR
Randomized trials (using rifampin)											
HK Chest Service[17‡]	Hong Kong	51	0%	167	161	74%	76%	7.8%	6.8%	15.0%	16.1%
Geiter[115]	USA, Canada	18–65	0%	132	131	63%	62%	1.5%	0%	nr	nr
Martinez *et al.*[§129]	Spain	34	0%	98	98	80%	90%	9.2%	7.1%	0%	1.0%
Martinez *et al.*[130]	Spain	34	100%	64	69	57%	63%	23.4%	7.2%	6.2%	2.9%
Rivero *et al.*[113]	Spain	32	100%	107	100	64%	63%	6.5%	10.1%	3.7%	4.6%
Rivero *et al.*[114]	Spain	32	100%	83	82	78%	84%	7.2%	18.3%	3.6%	3.7%
Whalen *et al.*[61]	Uganda	29	100%	536	556	88%	86%	0.6%	2.3%	1.3%	1.6%
Geijo *et al.*[131]	Spain	43	100%	45	51	76%	90%	4.4%	1.9%	2%	0%
Spyridis *et al.*[132]	Greece	9	0%	232	694	66%	84%	0%	0%	0%	0%
Randomized trials using INH & rifapentine											
Schechter *et al.*[134]	Brazil	37	0.2%	193[¶]	206	94%[¶]	93%	3.2%[¶]	0.5%	0.5%[¶]	1.46%
Non-randomized studies(using rifampin)											
McNab *et al.*[††133]	Canada	11	0	403	591	19%	82%	2.2%	6.6%	3.7%	0.3%
Jasmer *et al.*[‡‡94]	USA	52	<5%	545	477	80%	84%	3.7%	4.4%	1.1%	0.6%

[†] Number of subjects starting therapy in the INH or 3–4 months INH-RIF arms.
[‡] Hong study involved subjects with pulmonary silicosis.
[§] Martinez study: Patients received 9 months of INH.
[¶] Schecter study: The control arm was 2 months daily rifampin plus pyrazinamide (2RZ).
[††] McNab study: Patients received 12 months INH as daily and self-administered, or 6 months INH-RIF twice weekly under direct observation (DOPT).
[‡‡] Jasmer study: Patients received 12 months INH or 4 months INH-RIF—both daily and self-administered.
INH, isoniazid; nr: Outcome not reported; RIF, rifampin; TB, tuberculosis.

Thoracic Society[8]) was 4 months daily self-administered rifampin. As summarized in Table 7 there have been far fewer randomized trials using this regimen,[17,119,136,137] although several observational studies have been published in the last 5 years.[138–140]

The earliest published experience with this regimen was a placebo-controlled trial comparing three active regimens in older Chinese men with pulmonary silicosis, and a positive TST. In this trial, the regimen of 3 months daily rifampin was the best tolerated, with the best completion, and least adverse events (including no hepatotoxicity).[17] As shown in Figure 3 this regimen also was the most effective in preventing future active TB in this very high-risk population. However, the cumulative incidence of active TB during the 5 years of follow up after treatment was not significantly different between the three regimens; all were significantly better than placebo.

No subsequent randomized trial has evaluated effectiveness in preventing active TB. Two randomized trials have demonstrated significantly better completion rates with 4R than 9H,[105,137] and significantly lower rates of Grade 3–4 adverse events.[137] The difference was most notable for hepatotoxicity.[137] Several observational studies have consistently found that completion rates have been significantly better,[139,140] and serious adverse events, particularly hepatotoxicity significantly lower[139] with 4R compared with 9H. This experience is very different than the experience with 2RZ, and also compares favourably with the experience to date with 3–4 months HR.

Summary of acceptable alternative regimens

Given the evidence reviewed here, the 2RZ regimen should not be considered generally acceptable; this regimen should be reserved for carefully selected persons and in the unusual circumstances when a duration of only 2 months would be much more preferable than a duration of 3 or 4 months.

This leaves two acceptable alternative LTBI regimens, for which there is reasonable supportive published evidence. The first is the combination of INH and rifampin taken for 3–4 months. In randomized trials this regimen has similar completion to 6 months or more of INH, similar rates of adverse events, and, most importantly, similar protective efficacy. Whether the optimal duration is 3 or 4 months remains uncertain; therefore it would seem prudent to recommend 4 months of this therapy for most patients.

There is consistent evidence that 4 months monotherapy with rifampin is associated with better patient acceptability and compliance than 9 months INH. As well, there is consistent evidence—from randomized trials,[17,105,137] and observational studies,[139,140] that 4R is safer than 9H. In particular, the occurrence of hepatotoxicity has been much lower than with INH. This is very important, as this complication strongly affects the balance of risks and benefits in formal analyses,[141–144] and the informal (and less rational) risk–benefit analyses that influence patients' and providers' acceptance of LTBI therapy.

Table 7 Treatment completion, serious adverse events and rates of TB in Studies comparing 9 months isoniazid (9H) to 3–4 months RIF alone (3–4R)

Author (reference)	Study population				Completing therapy (%)		Serious adverse events (%)		Rates of active TB (cumulative %)	
	Country	Age (years, mean or range)	HIV (%)	Number†	9H	3–4R	9H	3–4R	9H	3–4R
				9H 3–4R						
Randomized trials										
HK Chest Service[17]	Hong Kong	51	0%	167‡ 165	74%	86%	7.8%	4.2%	15.0%	12.1%
Graczck *et al.*[119]	Poland	18–65	0%	88 95	68%	91%	0%	2.1%	0%	0%
Menzies *et al.*[105]	Canada	35	1%	58 58	62%	86%	10.3%	3.4%	nr	nr
Menzies *et al.*[137]	Canada, Brazil, Saudi Arabia	33	1%	427 420	76%	60%	4.0%	1.5%	nr	nr
Non-randomized comparative studies										
Polesky *et al.*§[138]	USA	36	5%	38 49	Nr	Nr	11%	14%	7.9%	0%
Page *et al.*[139]	USA	33	1%	770 1379	53%	72%	4.6%	1.9%	0%	0.1%
Lardizabal *et al.*[140]	USA	0–45	0%	213 261	53%	81%	6.1%	2.7%	nr	nr

† Number of subjects starting therapy in the isoniazid or 3–4 months rifampin arms ONLY.
‡ Hong study involved subjects with pulmonary silicosis. Patients received 6 months isoniazid.
§ Polesky study: Patients on rifampin received an average of 6.4 months of therapy.
nr, not reported; TB, tuberculosis.

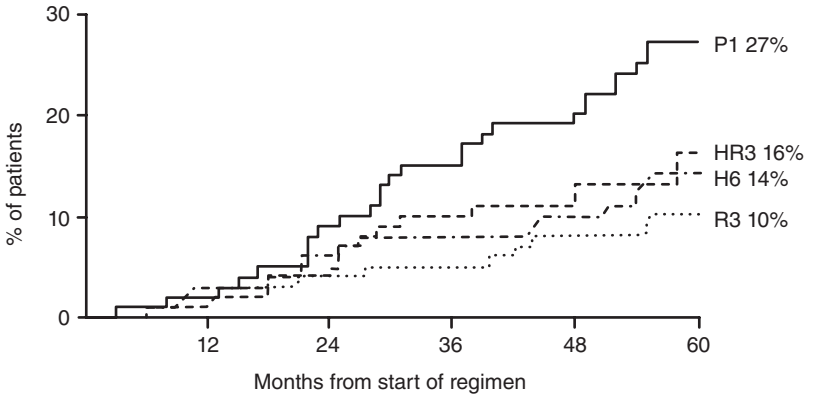

Figure 3 Effectiveness of three regimens for treatment of latent tuberculosis infection (LTBI) in elderly Chinese men with Silicosis (from Hong Kong Chest Service,[17] Am Rev Respir Dis 1992; 145:36–41). The *x*-axis shows the months from start of the LTBI treatment regimen. The *y*-axis shows the percentage of patients who developed TB disease. HR3, isoniazid and rifampin for 3 months; H6, isoniazid for 6 months; Pl, placebo; R3, rifampin for 3 months.

However, there are very limited data regarding the optimal duration of rifampin. In two case series, no patients developed active TB after taking 6 months rifampin,[138,145] compared with one case of active TB among 1379 persons treated with 4 months rifampin in a third-case series,[139] and only a 63% reduction of risk following 3 months rifampin therapy.[17] A large-scale international trial to assess the effectiveness of 4 months rifampin is now underway.

Which of the two acceptable regimens is preferable? The combination of INH-rifampin has the advantage of proven effectiveness, albeit in a limited number of relatively small trials. Importantly, in almost all of these trials the comparison was with 6 months INH;[135] this is less efficacious than 9–12 months INH.[3,59] In the only trial that compared rifampin alone with rifampin plus INH, the combination therapy was non-significantly worse.[17] And in the early experimental studies, bacillary clearance was as rapid with mono-rifampin therapy as clearance with rifampin combined with INH or pyrazinamide.[110] Hence it is not clear that the addition of INH improves the efficacy of 3–4 months rifampin. An important disadvantage is the additional toxicity of adding INH, particularly because the majority of serious adverse events, including hepatotoxicity, occur in the first 3 months of INH therapy.[105,137] It is known that patient adherence is lower with more complex regimens that involve a greater number of pills.[4,146] This may explain why completion of 3–4 months of INH and rifampin was not better than completion of a longer course of INH mono-therapy. Adding INH does offer theoretical protection against development of resistance if a person with undiagnosed active TB is inadvertently treated for LTBI. However, exclusion of active TB is an essential prerequisite for LTBI treatment, because all LTBI regimens are inadequate to treat active TB. In addition, given that spontaneous chromosomal mutations of *M. tuberculosis* leading to rifampin resistance are two to three orders of magnitude less frequent than to INH resistance (from[147]), a greater bacillary load is required before mono-therapy will be likely to generate resistance, making this scenario less likely.

TREATMENT OF LATENT TUBERCULOSIS INFECTION IN CONTACTS OF ACTIVE CASES WITH DRUG-RESISTANT TUBERCULOSIS

Treatment is generally recommended for persons with LTBI and recent close contact with a patient with infectious TB[48]. However, no treatment has been demonstrated to be efficacious for the treatment of LTBI caused by *M. tuberculosis* resistant to INH alone, nor to INH and rifampin (i.e. MDR).

For contacts of INH-resistant cases, there is reasonably good epidemiologic evidence that INH alone is not effective. In one observational study of contacts of INH-resistant cases, those who had taken INH had the same rate of INH-resistant active TB as persons who had not taken any therapy.[138] In another carefully followed cohort of Vietnamese refugees, the rates of INH-resistant active TB were the same in persons who completed INH therapy, as those who did not, but rates of INH-sensitive TB were much lower in the group who completed at least 6 months of INH.[148] There are no published trials of LTBI therapy in contacts of INH-resistant cases. A single case series, summarized in Table 7, described results with several therapeutic approaches to managing contacts of INH-resistant index cases in a prolonged outbreak in a Boston homeless shelter. Of those given INH, 7.8% developed INH-resistant active TB—virtually the same as the 8% rate in those who took no therapy. Yet none of 49 contacts who took 6 months rifampin alone, and none of 19 who took INH and rifampin for 6 months developed active TB.[138] Another case series described 157 TST-positive high-school students exposed to a highly infectious INH-resistant index case. Of those who completed 6 months rifampin, none developed active TB, when five cases were expected.[145] These limited observations support the current recommendations to use 4 months daily rifampin for contacts of contagious INH-resistant active TB cases.[8,48]

There is very little published evidence regarding therapy for contacts of patients with resistance to INH and rifampin (MDR-TB); hence recommendations for

their treatment are based on expert opinion (Table 8).[149,150] In 1992, CDC published initial guidance that recommended preventive therapy regimens with at least two antituberculosis drugs be strongly considered for persons likely to be infected with MDR *M. tuberculosis*, especially persons who have a high risk of developing active disease.[150] As potential regimens for treatment of MDR LTBI, CDC recommended either ethambutol and pyrazinamide or pyrazinamide and a fluoroquinolone if compatible with drug-susceptibility test results from the source case isolate of *M. tuberculosis*. Recently, the Francis J. Curry National Tuberculosis Center (San Francisco, CA, United States) published updated recommendations for potential treatment regimens.[149] Of note, these recommendations introduce the use of monotherapy with a fluoroquinolone and designate levofloxacin or moxifloxacin as the fluoroquinolones of choice.[149] The recommended duration for all MDR LTBI treatment regimens is 6–12 months.[149,150] Again, it is important to confirm that the isolate from the MDR-TB index (or source) case is susceptible to the drugs being prescribed when selecting a regimen.

In addition to the complete lack of data on the efficacy of regimens for treatment of MDR LTBI, studies on safety and tolerability are very limited. A report of 48 solid organ transplant recipients who were receiving levofloxacin and pyrazinamide for presumed MDR LTBI revealed that 32 (67%) discontinued therapy prematurely because of adverse events.[151] Gastrointestinal intolerance accounted for more than half of the adverse events. In a case series of 17 persons in Ontario, Canada with suspected MDR LTBI who were treated with levofloxacin and pyrazinamide, all 17 discontinued treatment because of a variety of adverse effects including musculoskeletal, central nervous system, gastrointestinal and dermatologic symptoms.[152] A report of a series of high-school students and teachers treated with ofloxacin and pyrazinamide after exposure to an infectious patient with MDR TB noted similar issues with frequent adverse effects.[153] Of 22 persons started on a 12-month course of therapy, only nine completed the course of medication. Hepatotoxicity was common, both symptomatic and asymptomatic. The alternative of ethambutol and pyrazinamide also appears to be poorly tolerated. Twelve contacts of two MDR-TB patients in Geneva, Switzerland were started on a 9-month course of ethambutol and pyrazinamide.[154] Only five (42%) completed treatment and the other seven discontinued medication because of hepatotoxicity. In reviewing these reports, it is not possible to be completely certain how many of the adverse effects were due to each individual drug versus the combination of the two. However, hepatotoxicity due to ethambutol is rare,[155] is uncommon with monorifampin therapy, as reviewed above, yet is very common with the 2 months rifampin/pyrazinamide. This evidence implicates pyrazinamide as the most likely cause of the reported high rates of intolerance of MDR LTBI regimens.[124] Given that flouroquinolones have been safe for MDR-TB treatment,[156] and in a few Phase-2 trials,[157] fluoroquinolone monotherapy or a fluoroquinolone in combination with ethambutol may be safer, better tolerated and increase the likelihood of completion.[149]

Table 8 Treatment of MDR LTBI (based on recommendations from CDC and Francis J. Curry National Tuberculosis Center[149,150]

Drug resistance pattern of source case isolate	Recommended regimen[†]
INH, RIF	FQN monotherapy or PZA and EMB or FQN and PZA or FQN and EMB
INH, RIF, EMB	FQN monotherapy or FQN and PZA
INH, RIF, PZA	FQN monotherapy or FQN and EMB
INH, RIF, EMB, PZA	FQN monotherapy or FQN and ethionamide
INH, RIF, EMB, PZA, ethionamide	FQN monotherapy or FQN and cycloserine
INH, RIF, PZA, EMB, and FQN	Cycloserine and PAS or PAS and ethionamide or ethionamide and cycloserine

[†] Recommendations are not evidence-based; there have been no clinical trials for the use of these regimens in contacts of patients with MDR TB. Recommendations are based on expert opinion.

FQN *in vitro* activity against M Tuberculosis strains: Moxiflixacin = Gatifloxacin > Levofloxacin >> Ofloxacin > Ciprofloxacin. Selection of FQN should take this activity into consideration (More active preferred).

CDC, Centers for Disease Control and Prevention; EMB, ethambutol; FQN, fluoroquinolone; INH, isoniazid; PAS, para-aminosalicylate; PZA, pyrazinamide; RIF, rifampin; TB, tuberculosis.

CONCLUSIONS AND RECOMMENDATIONS

As long as 9 months INH remains the standard therapy, LTBI treatment will remain expensive with a greater than desirable risk of adverse events and have suboptimal public health impact, because of poor acceptance by many patients and providers. At the moment, this regimen is considered the regimen of first choice, but two acceptable alternatives are 4 months of INH plus rifampin or 4 months rifampin mono-therapy. Of the two alternatives, the 2-drug regimen has been tested in more trials, and has equivalent completion, toxicity, and effectiveness as 6–9 months INH. Therapy with 4 months rifampin alone has significantly better completion, and significantly lower toxicity than INH. These are very important advantages, but effectiveness remains uncertain as this regimen has not been tested as extensively in randomized trails. Limited evidence from a mouse model, observational studies and one trial suggest that the mono-rifampin regimen is as effective as rifampin combined with INH. If this is confirmed in

ongoing studies, then 4 months mono-rifampin therapy may become the regimen of choice in the future. A final option is 3 months once weekly INH and rifapentine, which has been studied in a large-scale trial that is nearing completion; results are expected in 2012–2013.

DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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