Canadian Tuberculosis Standards

7th Edition

Chapter 6: Treatment of Latent Tuberculosis Infection

Public Health Agency of Canada
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CHAPTER 6

TREATMENT OF LATENT TUBERCULOSIS INFECTION

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KEY MESSAGES/POINTS

- Treatment of latent TB Infection (LTBI) can provide important individual and public health benefits – if given to people at high risk of developing active TB. This benefit has been demonstrated only in those with a positive tuberculin skin test (TST).

- Before treatment of LTBI is started, active disease must be excluded carefully by means of history, physical examination and chest radiography. Sputum samples should be sent for smear and culture, or other appropriate investigations should be performed if active disease is considered possible.

- The decision to treat LTBI should be individualized, with consideration of the risks of therapy from adverse events, such as hepatotoxicity, balanced against the risk of development of active disease.

- The current standard for treatment of LTBI is self-administered isoniazid (INH) taken daily for 9 months (9INH), as this shows the best evidence of efficacy.

- Acceptable alternatives include daily self-administered INH for 6 months (6INH), and daily self-administered INH and rifampin (RMP) for 3-4 months.

- Recent publications have reported good efficacy of a new regimen of 12 doses of INH and rifapentine (RPT) taken once weekly under direct observation. However, RPT is only available in Canada through the Special Access Program. If RPT is obtained through this program, clinicians should be aware that further evaluations of the regimen are needed, as adverse events are common, may be serious and are not well understood.

- Directly observed intermittent INH is an acceptable option in settings or populations in which completion rates of daily self-administered INH have been poor. The efficacy of this regimen is unclear although better than placebo in randomized trials. Use of other regimens, given intermittently, has not been studied adequately.

- Because of greater risk of hepato-toxicity in the post-partum period, treatment of LTBI should be deferred in pregnant women until 3 months postpartum unless they are at very high risk of disease (HIV-infected, close contacts, documented TST conversion). Treatment can be safely given to women who are breastfeeding.

- Contacts of patients with INH resistance (but not RMP resistance) should be treated with 4 months daily RMP (4RMP). Contacts of patients with RMP resistance (but not INH resistance) should be treated with 9INH. Contacts of patients with both INH and RMP resistance (but not fluoroquinolone resistance) can be offered therapy with levofloxacin or moxifloxacin daily for 9 months.

GENERAL CONSIDERATIONS

INTRODUCTION

After infection with *Mycobacterium tuberculosis* the risk of active tuberculosis (TB) development is influenced by the time since infection occurred, and the age and other medical conditions or therapies that affect the immune system of the person infected. Risk is highest in the first 1-2 years after infection. Risk is also high in very young children and declines rapidly in the first 5 years of life (see also Chapter 9, Pediatric Tuberculosis). In children, adolescents and adults a number of medical conditions that result in diminished immunity will increase risk of reactivation of latent infection.

The concept that mono-therapy with INH could successfully treat LTBI and prevent TB disease was first reported by Ferebee.[1] This was subsequently confirmed in more than 15 randomized trials involving more than 100,000 patients.[1] In these trials INH was effective, and excess toxicity was not detected. Because INH is also inexpensive it has become the standard first-line treatment of LTBI globally.[2-4]

RISK FACTORS FOR REACTIVATION OF ACTIVE DISEASE FROM LTBI

As summarized in Table 1, there are a large number of conditions that increase the risk of reactivation of active TB from LTBI. Many medical illnesses and therapies can increase the risk of reactivation, but the strongest risk factor is HIV infection. The other problems have in common a reduction or suppression of immune function and include diabetes, renal failure, malnutrition, certain cancers, alcohol overuse and cigarette smoking. Medical therapies that suppress immune function, listed in Table 1, are increasingly important indications for LTBI treatment.

Table 1. Risk factors for the development of active tuberculosis among people with a positive tuberculin skin test (presumed infected with *Mycobacterium tuberculosis)*

Risk factor	Estimated risk for TB relative to people with no known risk factor	Reference number
High risk		
Acquired immunodeficiency syndrome	110 - 170	5
Human immunodeficiency virus infection	50 - 110	6, 7
Transplantation (related to immune-suppressant therapy)	20 - 74	8 - 12
Silicosis	30	13, 14
Chronic renal failure requiring hemodialysis	7 - 50	15 – 18, 46, 47
Carcinoma of head and neck	11.6	19
Recent TB infection (≤2 years)	15.0	20, 21
Abnormal chest x-ray – fibronodular disease	6 - 19	22 - 24
Moderate risk		
Tumour necrosis factor alpha inhibitors	1.5 - 5.8	25, 26, 43
Diabetes mellitus (all types)	2 - 3.6	27 - 29
Treatment with glucocorticoids (≥15mg/d prednisone)	4.9	30
Young age when infected (0-4 years)	2.2 - 5	31
Slightly increased risk		
Heavy alcohol consumption (≥3 drinks/day)	3 - 4	32, 33
Underweight (<90% ideal body weight; for most people, this is a body mass index ≤20)	2 - 3	34
Cigarette smoker (1 pack/day)	1.8 - 3.5	35 - 38
Abnormal chest x-ray – granuloma	2	24, 39
Low risk		
Person with positive TST, no known risk factor, normal chest x-ray (“low risk reactor”)	1	40
Very low risk		
Person with positive two-step TST (booster), no other known risk factor and normal chest x-ray	0.5	Extrapolated from 40 and 1

TRANSPLANTATION

The immune suppression associated with prevention of rejection confers a risk of progression to active TB nearly as great as HIV infection, with an estimated incidence of over 500/100,000 annually in a Spanish cohort undergoing solid organ transplantation (crude risk ratio [RR] 26.6 compared with the general population).[8] Some clinicians may elect to initiate treatment under close supervision before liver transplantation in candidates with compensated cirrhosis, according to limited safety data.[41]

ANTI-TUMOUR NECROSIS FACTOR (ANTI-TNF) AGENTS

Anti-TNF agents currently licensed in Canada include adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®), golimumab (Simponi®) and infliximab (Remicade®). Etanercept is a soluble TNF receptor, which binds competitively with circulating TNF; the other agents are monoclonal anti-TNF antibodies.These agents are used for the treatment of autoimmune, inflammatory conditions, notably rheumatic diseases such as rheumatoid arthritis and inflammatory bowel disease.

Since the initial report of 70 patients in whom active TB developed after infliximab treatment[25] laboratory investigation has demonstrated that anti-TNF agents interfere with both innate and adaptive immune responses essential to containment of LTBI in granulomas.[42] The incidence of active TB appears to be markedly elevated in patients with rheumatoid arthritis (RA) who are administered these medications.[26] Comparing subjects who were receiving vs. those who were not receiving an anti-TNF agent, the RR of active TB after adjustment for age, sex, other comorbidities and other anti-rheumatic drug use was 1.5 (95% confidence interval [CI] 1.1-1.9) . However, a Spanish registry study comparing RA patients who received vs. those who did not receive an anti-TNF agent estimated a crude incidence rate ratio of 5.8 (95% CI 2.5-15.4).[43] It is clear that patients who begin anti-TNF treatment are at higher risk of TB disease than the general population. There are also limited observational data that suggest systematic screening and treatment of LTBI in these individuals successfully reduces the risk of active TB.[43]

CORTICOSTEROIDS

Systemic corticosteroids are administered for a variety of inflammatory conditions, either transiently for flares (as in asthma) or as long-term maintenance treatment (e.g. for rheumatic diseases). As with the anti-TNF agents, systemic corticosteroid use substantially increases the risk of active TB; the risk increases with the amount taken daily and with duration/cumulative dose. For example, patients receiving a daily dose of <15 mg prednisone had an adjusted odds ratio (AOR) of 2.8 (95% CI 1.0-7.9) for development of active TB compared with non-users, and for those taking a highest daily dose of ≥15 mg the AOR was 7.7 (2.9-21.4).[30] Although subjects received systemic corticosteroids for varying durations, risk was clearly elevated with even a single prescription. In another pharmacoepidemiologic study, the adjusted RR for active TB with systemic corticosteroid use (any dosage) was 2.4 (95% CI 1.1-5.4) among RA patients. Similar risks were observed in patients who were new users, defined as 90 days or less since first prescription.[44]

Use of inhaled corticosteroids is associated with more modest risk of active TB (adjusted rate ratio 1.48, 95% CI 1.11-1.97), although this finding was dose related, with an adjusted rate ratio of 1.97 (1.18-3.30) for the highest dose, i.e. ≥1,000 micrograms fluticasone equivalent daily.[45]

As with anti-TNF agents, everyone who is started on a regimen of systemic corticosteroids at daily doses of ≥15 mg prednisone equivalent for 1 month or longer should first be tested for LTBI. However, given the more modest effect of inhaled corticosteroids, screening for LTBI among users is not recommended.

CHRONIC RENAL FAILURE AND HEMODIALYSIS

Patients with end-stage renal disease receiving hemodialysis are at substantially elevated risk of active TB, with cited relative risks ranging from 7-50 times the background incidence.[46] A recent Greek study estimated an RR of over 30 after adjustment for age, body mass index and diabetes.[47] This relates to impaired immunity in the context of chronic uremia.

RADIOGRAPHIC SCARRING

Individuals with fibronodular scarring on chest radiography are at substantially increased risk of TB reactivation, in the absence of previous treatment. Estimated RRs range from 6 to 19.[22,24]

DIABETES

With the growing frequency of obesity and overweight in Canada, the prevalence of diabetes is increasing. It is estimated that over 2 million people in Canada carry the diagnosis of diabetes (over 6% of the Canadian population). Prevalence increases with age, particularly after age 40; the estimated prevalence now exceeds 20% in the 75-79 age group.[50] In addition, the prevalence of diabetes may be elevated in some immigrant and some Aboriginal populations, which also have a higher prevalence of TB infection (see Chapter 12, Contact Follow-up and Outbreak Management in Tuberculosis Control, and Table 1 in Chapter 13, Tuberculosis Surveillance and Screening in High-Risk Populations). For example, in a population-based Ontario study, immigrants from South Asia had an adjusted RR of diabetes of 3-4 compared with Canadian-born residents; among those from Latin America, the Caribbean and sub-Saharan Africa the RR was approximately 2.0.[51] A meta-analysis by Jeon and Murray estimated that active TB was 3 times more likely in diabetics than non-diabetics, after adjustment for age.[52] A more recent meta-analysis by Baker and colleagues estimated relative risks ranging from 1.7 to 5 for treatment failure, relapse and death among diabetics.[53]

CANCER

In a recent systematic review and meta-analysis of 18 studies of the risk of active TB development in patients with cancer, the risk compared with the general population was high (incidence rate ratio [IRR] 11.6; 95% CI 7.0-19.2).[19] The relative risk of active TB was markedly increased for all types of cancer although not significantly increased for solid tumours: risk for hematologic malignancies (IRR = 29.6 [11.6-75.7]), solid tumours (IRR = 17 [0.7-391]) and stem cell transplants for hematologic malignancies or hematologic disorders (IRR = 5.3 [2.6-10.9]). The risk of TB in patients with head and neck cancer is difficult to quantify as the studies describing this relationship were not comparable with each other or with other studies included in the review, and the reported cumulative incidence took place over variable periods of time rather than being an annual risk of disease.[54-56]

On the basis of these findings, patients with all types of hematologic malignancies and bone marrow transplant for hematologic malignancy should be offered screening for LTBI, but there is insufficient evidence to offer LTBI screening and treatment to patients with solid tumours.

TOBACCO AND ALCOHOL

Tobacco smoking is associated with increased risk of LTBI (estimated RR 1.7-1.9), active TB disease (RR 2.0-2.7) and death from TB (RR 2.6), according to two recent meta-analyses.[35-37] Another recent meta-analysis suggested that heavy alcohol use (>40 g/day) is also associated with an increased risk of active TB (RR 2.9, 95% CI 1.9-4.6).[57]

INDICATIONS FOR TREATMENT OF LTBI

For consideration of LTBI treatment in an individual patient the risk factors reviewed above and listed in Table 1 are important, as the degree of risk will determine the potential benefit from LTBI treatment. There are two categories of indications for LTBI treatment: recent infection and increased risk of reactivation. Reactivation risks have been considered above; recent infection is common in contacts of patient with active contagious TB (see also Chapter 12). This is also seen in people with documented TST conversion from negative to positive (see Table 2; see also Chapter 4, Diagnosis of Latent Tuberculosis Infection), such as health care workers.

Table 2. Tuberculin skin test cut-points for treatment of latent TB infection

TST result	Indication*
0-4 mm	In general this is considered negative and no treatment is indicated.†
	Close contacts in children less than 5 years of age should be treated pending results of repeat skin test 8 weeks after exposure. ‡
≥5 mm	HIV infection
	Contact with infectious TB within the past 2 years
	Fibronodular disease on chest x-ray (healed TB and not previously treated)
	Organ transplantation (related to immune suppressant therapy)**
	TNF alpha inhibitors
	Other immunosuppressive drugs, e.g. corticosteroids (equivalent of ≥15 mg/day of prednisone for 1 month or more; risk of TB disease increases with higher dose and longer duration)
	End-stage renal disease
≥10 mm	TST conversion (within 2 years)
	Diabetes, malnutrition (<90% ideal body weight), cigarette smoking, daily alcohol consumption (>3 drinks/day)
	Silicosis
	Hematologic malignancies (leukemia, lymphoma) and certain carcinomas (e.g. head and neck)

*Age ≥35 years is *not* a contraindication to treatment of LTBI if the risk of progression to active TB disease is greater than the risk of serious adverse reactions to treatment.

†Treatment with INH of people with HIV infection who were TST negative (0-4 mm) and/or anergic was of no benefit in several randomized trials. Other authorities suggest this treatment may be considered in the presence of HIV infection or other cause of severe immunosuppression AND high risk of TB infection (contact with infectious TB, from high TB incidence country or abnormal chest x-ray consistent with prior TB infection). Hence any decision to give treatment should be individualized in consultation with a TB expert.

‡If first TST is negative, begin treatment immediately. Repeat TST 8 weeks after exposure to infectious TB case ended. Treatment can be stopped in a healthy child if repeat TST is negative (<5 mm induration). In children <6 months of age, the immune system may not be mature enough to produce a positive TST, even if the child is infected (See Chapter 9, Pediatric Tuberculosis).

**LTBI therapy is often given to people in whom transplantation is planned but before the actual transplantation.

However, if considered from a public health perspective, treatment of some of these high-risk conditions will have little impact at a population level. This is because the total number of cases attributable to each of these conditions is determined by not only the risk but also the prevalence of the condition. As summarized in Table 3, the World Health Organization has estimated that some widely prevalent conditions contribute more cases than HIV infection to the global burden of TB.[58] Hence, if LTBI treatment of everyone who is malnourished, has diabetes or smokes cigarettes were possible, then this would have the greatest public health impact.

Table 3. Impact of risk factors on the global burden of tuberculosis
(adapted from Lonnroth et al.[58])

Risk factor	Relative risk (compared with healthy person)	Population attributable fraction
HIV infection	35-110	11%
Malnutrition	2-3	27%
Diabetes	3-4	8%
Alcohol abuse	2-3	10%
Cigarette smoking	2-2.5	16%

LTBI TREATMENT IF IMMUNE COMPROMISED AND TST IS NEGATIVE

Multiple randomized trials have compared INH with placebo in HIV-infected individuals who are TST positive or TST negative. Five of these trials were summarized in a meta-analysis. The pooled estimate of reduction in disease compared with placebo was 14% in HIV-infected individuals who were initially TST negative and more than 60% in those who were initially TST positive; the latter finding was significant.[59] These findings were recently confirmed in a large-scale trial in Botswana, in which benefit of INH for 36 months was demonstrated only in those with initial TST of 5 mm or greater (positive).[60] Two trials have compared rate of disease following INH or placebo in HIV-infected individuals who had no response to tuberculin antigens (i.e. were TST negative) or to a panel of common antigens (i.e. were anergic).[61,62] In both trials there was no significant benefit of INH treatment.

Hence, based on these studies, LTBI therapy is not indicated for individuals who are immune compromised and TST negative. In certain circumstances a severely immune compromised patient may be considered at such a high risk of infection and subsequent disease that LTBI treatment may be given presumptively, even with a negative TST or in the absence of a TST. Such treatment should be carefully considered by balancing the risks and benefits on an individual basis.

ADVERSE EVENTS OF THE DRUGS USED TO TREAT LTBI

(See Chapter 5, Treatment of Tuberculosis Disease.)

RECOMMENDATIONS FOR TREATMENT

Recommendations for LTBI treatment are summarized in Table 4. The evidence, from randomized trials, in support of these recommendations is summarized in Table 5.

STANDARD REGIMEN

The standard regimen of first choice is 9 months of daily self-administered INH (9INH).
(Strong recommendation, based on strong evidence)

INH is still considered the standard first-line therapy, given its long history of use, well- known safety profile and demonstrated efficacy in multiple randomized trials conducted in HIV-infected[59,80] and HIV-uninfected populations[1,81] in many settings.

INH is usually self-administered daily. The optimal duration based on a reanalysis by Dr. George Comstock of data from trials among Alaskan Inuit appears to be 9 months.[71] In this reanalysis, protective efficacy against reactivation of TB progressively increased with longer duration of INH, up to a maximum of 90% with 9 months' therapy; there was no further improvement in efficacy with longer duration of therapy.[71]

Pyridoxine (vitamin B6) should be given to minimize the risk of neuropathy in people with risk factors for pyridoxine deficiency (such as malnourished or pregnant individuals) or for neuropathy (patients with diabetes or renal insufficiency). B6 supplements are not routinely needed otherwise.[3]

INH treatment is associated with two major problems. The first is toxicity, particularly hepatotoxicity, which can be fatal. The second problem is the long duration. These two problems result in poor acceptance of this therapy by patients and providers, and poor completion rates by patients. As a result there has been substantial interest and research in shorter regimens that are safer than and at least as effective as INH.

SHORTER ALTERNATIVE REGIMENS

Six months of daily, self-administered INH (6INH) is an acceptable alternative.
(Strong recommendation, based on strong evidence)

This regimen has been documented to achieve better completion rates but has a protective efficacy of only 67%[73] or 69%.[63] In Canada 6INH should be considered a regimen of second choice, even if this regimen is recommended by authorities elsewhere.[4]

Three or 4 months of daily, self-administered INH and RMP (3-4INH/RMP) is also an acceptable alternative.

(Strong recommendation, based on strong evidence)

A number of randomized trials have compared the efficacy and safety of daily self-administered INH and RMP taken together for 3-4 months. These results have been summarized in a recent systematic review meta-analysis, which found that the efficacy and safety of this regimen was similar to 6 to 9 months of INH.[82]

Three months of once weekly, directly observed INH and RPT (3INH/RPT) has acceptable efficacy, but because of high rates of poorly understood hypersensitivity reactions should be used only with very close monitoring.

(Conditional recommendation, based on moderate evidence)

RPT is a rifamycin with a half-life that is 5 times longer than that of RMP. Hence, it can be given as infrequently as once weekly.[69] The 3INH/RPT regimen has been assessed in three randomized trials. In these trials every dose was directly observed, whereas the comparator regimen of INH was self-administered daily. The first, conducted in Brazil, found that this regimen was slightly but not significantly worse than 6 months of INH in preventing active disease among close contacts, with similar toxicity.[79] The second, published in 2011, was conducted in South Africa and reported similar efficacy and toxicity but better completion than 6INH.[74] The third and largest trial involved more than 8,000 mostly HIV-uninfected individuals in the United States, Canada and Spain. In this trial the 3INH/RPT regimen was as efficacious as 9INH, with significantly better completion rates and significantly less hepatotoxicity.[69] Interestingly, the overall rate of serious adverse events was actually higher with the 3INH/RPT regimen because of an excess occurrence of hypersensitivity reactions.[69]

In summary, the evidence to date indicates that this is a very promising regimen that is well accepted, has high completion rates and shows efficacy that is similar to that of 9 months of INH. However, every dose should be directly observed, which can be difficult to organize in some practice settings or populations. More importantly, the occurrence of hypersensitivity reactions, which can be severe, is unexplained. Until this problem is better understood the regimen should be used ONLY under carefully monitored circumstances; patients who are prescribed this regimen should be questioned carefully, before administration of each dose, about any problems that were related to the preceding dose. Therefore, the regimen is not recommended at this time for general use. It is hoped that these adverse reactions will be better understood with more use of the regimen, allowing them to be prevented and/or managed more easily. A second barrier is that RPT is only available in Canada through the Special Access Program (http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/sapg3_pasg3-eng.php).

Four months of daily, self-administered RMP (4RMP) can be used as an alternative, given excellent safety but uncertain efficacy.

(Conditional recommendation, based on moderate evidence)

In the United States and Canada 4RMP has been recommended as an alternative regimen since 2000.[2,3] Experience with the regimen under program conditions has been good; completion rates have been substantially and significantly better than for 9INH with very low

toxicity, particularly hepatotoxicity.[83,84] Two randomized trials have demonstrated superior completion and lower adverse event rates.[68,77] To date, a single randomized trial has evaluated the efficacy of this regimen:[13] 3 months of RMP were compared with 6 months of INH , 3 months of INH/RMP, and placebo. A 63% reduction in disease was achieved with 3RMP, better than the other two regimens and significantly better than placebo.[13] There are no published data on the efficacy of 4RMP, although a large-scale international trial comparing the efficacy of 4RMP and 9INH is ongoing; the results will only be available in 2016. It is anticipated that the efficacy of 4RMP should be better than that of 3RMP, making it close to that of 9INH. Given the consequences of RMP resistance, careful exclusion of active TB is even more important if this regimen is used.

Two months of daily, self-administered rifampin/pyrazinamide (2RMP/PZA) should NOT be used.

(Strong recommendation, based on strong evidence)

In 1989 this regimen was reported to be highly effective in a mouse model of LTB.[85] Several randomized trials were subsequently conducted comparing this regimen with placebo or INH (with varying duration) in HIV-infected populations.[61,73,75] The 2RMP/PZA regimen had efficacy and toxicity similar to those of the comparator INH regimens. Following recommendations for the use of 2RMP/PZA[3] the regimen was adopted enthusiastically by providers and patients. Within a year numerous reports were published of severe, even fatal, hepatotoxicity with use of 2RMP/PZA.[86,87] This led to revised recommendations to restrict its use.[88,89] The regimen is not recommended in Canada.

INTERMITTENT REGIMENS

To enhance the feasibility of directly observed therapy, intermittent LTBI regimens have been assessed in a few randomized trials. Given twice weekly, 6INH resulted in significant reduction of disease compared with placebo in two trials in HIV-infected individuals.[75,76] In the only published trial that has directly compared intermittent with daily INH, thrice weekly 6INH was somewhat less effective than daily 6INH in HIV-infected children.[91] This difference was not significant, but statistical power was limited because the trial was stopped early as a result of a very high rate of disease in the placebo arm. Twice weekly directly observed INH and RMP for 6 months was significantly superior to daily self-administered INH for 12 months in a non-randomized observational study in Saskatchewan.[91]

On the basis of this limited evidence it appears that intermittent regimens with INH offer some benefit relative to nothing (placebo control), but their efficacy relative to daily INH has not been adequately assessed.

Hence, intermittent, directly observed regimens with INH or INH/RMP should be considered alternative regimens and used in selected circumstances or populations where daily, self-administered regimens have had limited success.

(Conditional recommendation, based on weak evidence)

As with active TB, all doses of intermittent regimens for LTBI should be directly observed.

Table 4. Summary of recommended regimens for LTBI treatment

Drug(s)*	Duration	Schedule	Mode of administration	Level of evidence†
Standard regimen				
INH	9 months	Daily	SAP	1
Acceptable alternative regimens				
INH	6 months	Daily	SAP	1
INH/RMP	3 months	Daily	SAP	1
INH/RPT‡	3 months	Once weekly	DOP	1
RMP	4 months	Daily	SAP	2
INH	6-9 months	Twice weekly	DOP	2
INH/RMP	3 months	Twice weekly	DOP	2

INH = isoniazid, RMP = rifampin, RPT = rifapentine, SAP = self-administered prophylaxis, DOP = directly observed prophylaxis.

*For doses of these drugs see Chapter 5.

†Evidence for each regimen is summarized in Table 5. Level 1: multiple randomized trials; Level 2: single randomized trial and/or multiple observational (cohort) studies.

‡Use this regimen with careful monitoring for hypersensitivity reactions – these can be severe. RPT is only available in Canada through the Special Access Program.

Table 5. Summary of evidence to support recommendations
(data taken only from published randomized trials)

Regimen	Duration	Completion	Adverse events	Efficacy*
INH (Daily)	12 months	68%[63] 69%[64] 85%[65]	5.2%[63] 6.1%[64]	67%[66] 93%[63]
	9 months	57%[67] 60%[68] 62%[63] 69%[69] 86%[70]	0†[70] 3.7%[69] 4.0%[68]	90%[71]
	6 months	63%[61] 65%[72] 73%[13] 75%[73] 78%[63] 84%[74]	0.6%[73] 1.9%[74] 2.8%[61] 3.6%[63] 7%[72] 8%[13]	67%[63] 68%[73]
INH (Twice weekly)	6 months	55%‡[75] 72%‡[76]	0[75] 3%[76]	Eq2RMP/PZA[75] 40%[76]
RMP (Daily)	4 months	76%[13] 80%[68] 86%[77]	0[13] 1.5%[68]	63%[13]
INH/RMP (Daily or twice weekly)	3 months	63%[67] 69%[72] 75%[73] 76%[13] 95%‡[74] 97%[78]	0‡[70] 2.3%[73] 3.8%[74] 5%[13] 7%[78] 10%[67] 18%[72]	64%[73] Eq6INH[13,72,74] Eq9INH[67] Eq12INH[78]
INH/RPT** (Once weekly)	3 months	82%‡[69] 95%‡[79] 96%‡[74]	1.0%[79] 1.8%[74] 4.9%[69]	Eq 2RMP/PZA[79] Eq 6INH[74] Eq 9INH[69]

INH = isoniazid, RMP = rifampin, PZA = pyrazinamide, RPT = rifapentine, Eq = equivalent to,

12INH = 12 months INH, 9INH = 9 months INH, 6INH = 6 months INH, 2RMP/PZA = 2 months RMP & PZA

*Efficacy estimated from placebo controlled trials or listed as (EqNx), meaning equivalent to the comparator regimen. Estimates shown are for TST-positive patients if these results are provided.

†Study in children

‡Halsey et al.:[75] half of the doses were supervised. Mwinga et al:[76] fully supervised treatment (DOPT).

**RPT available in Canada only through Special Access Program, see text.

OLDER AGE AND LTBI TREATMENT

There is a well-recognized relationship between older age and greater risk of adverse events, particularly hepatotoxicity, during treatment with INH. This relationship was noted in the 1970s[92,93] and in more recent studies.[94,95] In one of the earliest surveillance studies mortality from INH hepatitis was reported only in individuals over the age of 35.[93] This well-known but post-hoc analysis has resulted in the common misconception that only patients under 35 should be treated. However, there is no age at which there is zero risk – hepatotoxicity has been reported in young children,[96] although this is rare (<1 per 1,000). In a recent study patients over the age of 50 had increased rates of hospitalization attributable to liver toxicity from INH.[95] In patients 65 and older, 2.6% were hospitalized for INH-associated hepatotoxicity. The greatest risk of hepatotoxicity was in the elderly with comorbidities; those without comorbidities under the age 65 had low rates of hepatotoxicity that were not age dependent.[95]

As shown in Table 6, the number of patients needing to be treated before harm, rather than good, is caused is more than 100 in those aged under 35, but falls within the range of 9-15 in the elderly.

Patients who are under 65 years old and have no comorbidities should be offered LTBI treatment if they are at moderate or higher risk.

(Conditional recommendation, based on moderate evidence)

However, the risks and benefits should be considered very carefully in people over the age of 65, although therapy may be reasonable in those at high risk of reactivation and without comorbidities. At any age the risk of toxicity should be weighed against the benefit of therapy. In older people with greater risk of toxicity, therapy is indicated only if the risk of disease is high, meaning that they must have recent infection or medical risk factors for reactivation. As an example, a 25-year-old healthy individual with no risk factors for reactivation (detected through pre-employment screening) may be considered for LTBI treatment, but the risks might exceed the benefits if, instead, they were 45 years old. However, the benefits of INH therapy will exceed the risks of toxicity at almost any age in an HIV-infected individual. The reader is referred to a useful on-line tool that may assist in the assessment of likely risk of disease and adverse events in an individual (see: http://www.tstin3d.com).

Table 6. Estimated number needed to harm with isoniazid treatment for LTB, with increasing risk of INH hepatotoxicity
(derived from published toxicity estimates)

Age range	Incidence of hepatotoxicity (%)	Number*	95% Confidence interval
<20 yr	0.10	268	69-2513
	0.20	134	35-1256
20-34 yrs	0.25	107	28-1005
35-49 yrs	0.5	54	14-503
	0.75	36	9-335
50-64 yrs	1.0	27	7-251
	1.25	21	6-201
	1.50	18	5-168
	1.75	15	4-144
≥65 yrs	2.0	13	3-126
	2.25	12	3-112
	2.5	11	3-101
	2.75	10	3-91
	3.0	9	2-84

Risk of hepatotoxicity increases with age:
<20 yr: 0.1%-0.2%[97-103]
20-34 yr: 0.3%[104-106]
35-49 yr: 0.5%[104-106]
50-64 yr: 1%-3%[104-106]
≥65 yr: 2%-5%[95,107,108]

* Number of patients needing to be treated before harm, rather than good, is caused.

PREGNANCY OR BREASTFEEDING AND LTBI TREATMENT

INH and RMP are considered safe in pregnancy, although the mother should be given pyridoxine (vitamin B6) supplements.

(Strong recommendation, based on moderate evidence)

An increased risk of hepatotoxicity from INH has been reported in women treated during the first 3 months postpartum.[109]

Hence, deferral of treatment of LTBI until 3 months after delivery is recommended unless there is very high risk of development of disease, such as HIV infection or recent infection.

(Conditional recommendation, based on weak evidence)

Breastfeeding is considered safe for mothers taking INH or RMP, and they should also take pyridoxine (vitamin B6) supplements. Approximately 3% of the maternal dose is excreted in breast milk.[110] This means that even a newborn will not be exposed to a significant dose of INH.

DURATION OF THERAPY (IN HIV-INFECTED INDIVIDUALS)

In settings with a very high incidence of TB disease and accordingly high rates of transmission of TB infection, the benefits of INH therapy for LTBI have not extended far beyond the end of therapy in HIV-infected people. Several trials have examined a longer duration of INH. In Botswana, TST-positive, HIV-infected individuals were randomly assigned to 36 months of INH (36INH) or 6INH followed by 30 months of placebo.[60] The 36INH regimen was associated with substantially and significantly lower rates of disease, but only in subjects who were initially TST positive.[60] In a second study in South Africa, lifelong INH in TST-positive, HIV-infected people was more efficacious than 6INH.[74] However, adverse events were much more common, and compliance fell progressively over time.[74] In Canada such high transmission rates are rarely, if ever, encountered (see: http://www.phac-aspc.gc.ca/tbpc-latb/pubs/tbcan10pre/index-eng.php).

Prolonged therapy with INH, beyond the standard 9 months, is not recommended in Canada.

(Strong recommendation, based on moderate evidence)

TREATMENT OF PRESUMED DRUG-RESISTANT LTBI

(See also Chapter 8, Drug-Resistant Tuberculosis.)

The question of how to treat presumed drug-resistant (DR) LTBI usually arises in patients who are close contacts of index cases with known drug-resistant TB. There have been no randomized trials of treatment of contacts of any form of DR-TB. Hence, all the recommendations in Table 7 are based on expert opinion rather than evidence of efficacy.

Table 7. Recommended regimens for contacts of drug-resistant index cases

Drug resistance pattern of index case	Recommended regimen*	Level of evidence†
PZA and/or EMB	9INH	1
Mono INH	4RMP	2
Polydrug resistance including INH	4RMP	1
Mono RMP resistance (INH susceptible)	9INH	1
MDR (INH and RMP resistant)	9 FQN: levofloxacin or moxifloxacin	4

PZA = pyrazinamide, EMB = ethambutol, INH = isoniazid, RMP = rifampin, 9INH = 9 months daily INH, 4RMP = 4 months daily rifampin, 6FQN = 6 months daily fluoroquinolone

*All regimens are suggested to be self-administered and taken daily.

†Level of evidence: 1 = multiple randomized trials, 2 = single trial and multiple observational studies, 4 = expert opinion only.

Simply stated, contacts of patients with INH resistance (but not RMP resistance) should be treated with 4RMP.

(Conditional recommendation, based on weak evidence)

Contacts of patients with RMP resistance (but not INH) should be treated with 9INH.

(Strong recommendation, based on strong evidence)

For contacts of patients with multidrug-resistant (MDR) TB, a combination of a later generation fluoroquinolone (FQN) and pyrazinamide (PZA) has been recommended.[3] However, two case series reported very high rates of toxicity and intolerance, and very poor completion rates with this regimen, possibly as a result of the effects of PZA.[111,112]

Daily use of levofloxacin or moxifloxacin for 9 months (*conditional recommendation, based on very weak evidence*) **is recommended**, based on evidence that later generation FQN are generally well tolerated and can adequately replace INH in active TB therapy.[113] However, the tolerability and safety of long-term use of FQN are not well known; patients should be advised of this and monitored closely for adverse events.

Contacts presumably infected with an MDR-TB isolate should be thoroughly educated about symptoms and signs of TB, and the need for immediate medical evaluation if symptoms occur. Because of the limited amount of information about the efficacy of preventive therapy in individuals likely to be infected with an MDR-TB strain, contacts should be followed closely for the 2 years immediately after infection. Contacts of MDR-TB patients who do not accept or tolerate TB preventive therapy or in whom there is no preventive therapy (the source case isolate is resistant to all first- and second-line drugs) should be carefully followed over a period of 2 years (e.g. at 6, 12 and 24 months) for the appearance of signs and symptoms of active disease.

THERAPY IF THERE IS RENAL OR LIVER DISEASE

Therapy for LTBI with INH or RMP does not need to be adjusted for renal insufficiency.[2,3]

Mild hepatic dysfunction is a relative contraindication for INH therapy. In such patients, RMP may be a better choice than INH in view of its lower hepatotoxicity in randomized trials[13,68] and observational studies.[83,84] In patients with severe hepatic dysfunction, INH, RMP and RPT should be avoided altogether. Instead, daily levofloxacin or moxifloxacin for 9 months may be used on the basis of evidence that these agents can replace INH in therapy of active TB;[113] their efficacy for LTBI is unknown. Generally, these agents are very well tolerated, although in a recent report their use was associated with an incidence of hepatotoxicity of approximately 4 per 100,000.[114]

FOLLOW-UP AND MONITORING DURING LTBI THERAPY

For patients receiving self-administered treatment of LTBI the prescription for medication should not exceed a 1-month supply of doses. Exceptions can be made, such as if a patient is travelling.[2,3]

There are two main objectives of follow-up during LTBI therapy: (i) early detection and management of adverse events; and (ii) monitoring and enhancing compliance. Practice varies widely, but contact with patients is recommended every month, at least by telephone if not in person.[2,3] Monitoring of liver function tests is controversial, but the consensus of expert opinion is reflected in Table 8 (all the recommendations in Table 8 are conditional, based on expert opinion, i.e. very weak evidence). If liver transaminases increase beyond 5 times the upper limit of normal (or 3 times in the presence of symptoms) the LTBI regimen should be stopped. (Detailed suggestions for management of adverse events are found in Chapter 5: Treatment of Tuberculosis Disease.)

Adherence can be monitored in several ways. Patients' self-report is notoriously unreliable, as is health care provider assessment.[115] Pill counts are somewhat more reliable, although patients can discard pills rather than swallow them. Urine tests can be performed to detect INH or RMP metabolites. Devices that monitor each time that doses are withdrawn from pill bottles are the most reliable,[116,117] but expensive; simple, reliable devices are still under development. At present there is no perfect way to monitor adherence.

It has been observed that there are large differences in rates of completion of LTBI therapy between programs. Programs with higher rates of completion emphasize patient-centred care, with close follow-up, frequent reminders of the importance of therapy and constant encouragement to complete therapy.[3]

Although rare, severe hepatotoxicity requiring transplantation or leading to death has occurred during INH treatment of LTBI.[118] Therefore, it is recommended that patients receiving INH therapy should be provided with a clear written plan of action, including contact telephone numbers, should symptoms arise.

This plan, which should be reinforced by the prescribing health care provider, should recommend that patients contact their health care provider *immediately* if they have symptoms such as anorexia, nausea, vomiting, abdominal discomfort, unexplained fatigue, dark-coloured urine, scleral icterus or jaundice. If they cannot reach their provider they should stop the INH until they have been seen and evaluated. Evaluation should include a physical examination and investigation of liver transaminase values and bilirubin levels.

Table 8. Suggested follow-up schedule for patients receiving 9INH latent TB treatment*
(Conditional recommendations, based on very weak evidence)

Actions	Start of treatment	1 month	2 month	3 month	4 month	5 month	6 month	7 month	8 month	9 month
Medical evaluation	X	X	X	If needed	X	If needed	X	If needed	X	If needed
Telephone call to patient				X		X		X		X
Compliance assessment		X	X	If needed	X	If needed	X	If needed	X	If needed
Chest radiography	X									
Bilirubin, transaminases										
Age <35	If clinical suspicion of liver disease	If needed	If needed	If needed	If needed	If needed	If needed	If needed	If needed	If needed
Age 35-50	X	X	If needed		If needed		If needed		If needed	X
Age >50 or other risk factors†	X	X	X	X	X	X	X	X	X	X

*Schedule is for treatment with 9INH. If alternative regimen is used, suggest same schedule until end of therapy. All recommendations in this table are based solely on expert opinion.

†These include pregnancy or first 3 months postpartum, history of previous drug-induced hepatitis, current cirrhosis or chronic active hepatitis of any cause, hepatitis C, hepatitis B with abnormal transaminases, daily alcohol consumption or concomitant treatment with other hepatotoxic drugs (e.g. methotrexate). HIV infection is not an independent risk for drug-induced hepatitis.

DOCUMENTATION OF TREATMENT OF LTBI

The drug, dosage, interval (daily, 2x/wk, 3x/wk), mode (directly observed or self-administered), start date, end date and total number of doses taken should be recorded.

FOLLOW-UP AFTER LTBI TREATMENT AND MANAGEMENT FOLLOWING RE-EXPOSURE

There is no need for routine follow-up after completion of LTBI treatment. If a patient refuses or does not complete therapy, then he or she should be instructed carefully regarding the principal symptoms of active TB and instructed to return for evaluation if those symptoms arise.

Routine chest radiography has very low yield and is not recommended (see Chapter 3: Diagnosis of Active Tuberculosis and Drug Resistance). If patients are re-exposed through contact with a case of active contagious TB, there is no value in repeating the tests for LTBI infection ("once positive = no longer useful"[119]).

In immunocompetent people there is evidence that a first episode of TB infection provides approximately 80% protection against development of disease following re-exposure.[120] This benefit is similar to that achieved with 9 months of INH therapy.[71]

Hence, a second course of LTBI treatment is not recommended, even if the re-exposure was close/intense and even if exposure was to a drug-resistant case.

(Conditional recommendation, based on very weak evidence)

However, if there is uncertainty that a previous course of LTBI therapy was taken adequately, then it may be prudent to recommend the patient take a full course of LTBI therapy.

(Conditional recommendation, based on very weak evidence)

In immune compromised individuals, such as HIV-infected people or very young children (under 5), there may not be any effective immunity conferred by prior TB infection.

Therefore, it is recommended that these individuals could be considered for a second course of LTBI treatment.

(Conditional recommendation, based on very weak evidence)

However, this recommendation is not based on any published evidence that such treatment is effective, nor is there broad consensus on the benefits of retreatment of LTBI following re-exposure. Further considerations include how well the individual tolerated previous LTBI treatment, likely adherence to another course of treatment and probable public health consequences if active TB develops.

DOES TREATMENT OF LTBI CREATE DRUG RESISTANCE?

This is a commonly asked question, particularly when dealing with a population with historically low rates of LTBI treatment completion. A systematic review of 13 randomized trials found that the rate of disease with INH-resistant strains was somewhat but not significantly higher in those assigned to INH than to placebo.[121] In a subsequently published trial among HIV-infected people, those assigned to 36 months of INH had a similar rate of INH-resistant TB as the group assigned to 6 months of INH.[60]

As well, a large cohort study in the United States found no evidence of increased INH resistance, simply that INH was ineffective in preventing INH-resistant TB.[122] In all studies disease was most likely to develop in those who did not complete INH; hence, the evidence is consistent that INH therapy of LTBI, even when inadequately taken, does not lead to the emergence of resistance. Of course, in all these studies active disease was carefully excluded before mono-INH was begun.

PROGRAM INDICATORS

The ideal LTBI treatment delivery program will achieve, at a minimum, 80% acceptance of treatment among people with LTBI in whom treatment is indicated, and at least 80% of those starting will complete the required number of doses.[2,3]

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