ERJ Express. Published on August 6, 2010 as doi: 10.1183/09031936.00079310

TREATMENT OF LATENT INFECTION WITH *M. TUBERCULOSIS*: UPDATE 2010

Chi Chiu Leung
Tuberculosis & Chest Service, Department of Health, Hong Kong, CHINA

Hans L Rieder
International Union against Tuberculosis and Lung Disease, Paris, FRANCE and Institute of Preventive and Social Medicine, University of Zurich, Switzerland

Christoph Lange
Division of Clinical Infectious Diseases, Medical Clinic, Research Center Borstel, Borstel, GERMANY

Wing Wai Yew
Tuberculosis & Chest Unit, Grantham Hospital, Hong Kong, CHINA

Correspondence:
Chi Chiu Leung
Wanchai Chest Clinic, 99 Kennedy Road, Wanchai, Hong Kong, China
Email: cc_leung@dh.gov.hk
Tel.: 852-25353864, Fax:852-29775940

Word Count: 10638

Abstract

Much remains unknown about latent infection with *Mycobacterium tuberculosis*. Existing immunodiagnostic tools for this condition have various limitations, most importantly in their ability to predict disease. Randomized controlled trials have established protective efficacy of isoniazid therapy for 6 to 12 months among non-HIV-infected and HIV-infected subjects. While efficacy may reach 90%, acceptance and adherence to prolonged therapy are less than desired. Rifampicin plus pyrazinamide for two months, though efficacious, has been associated with excess hepatotoxicity in non-HIV infected persons. Isoniazid plus rifampicin for 3 months has proven efficacy, but adverse effects may be more frequent than isoniazid or rifampicin monotherapy. Rifampicin monotherapy for 3 to 4 months is well tolerated, but efficacy data are currently limited, and concerns remain over possible selection of rifampicin-resistant mutants. For contacts of patients with multidrug-resistant tuberculosis, expert opinions differ on whether to treat, with at least two drugs or just a fluoroquinolone, and for how long. With the existing diagnostic and treatment tools efficacy of preventive therapy does not necessarily translate into field effectiveness. A targeted approach is required to maximize cost-effectiveness. Each geographic region needs to set its own priority after taking into account available scientific data and local circumstances.

Introduction

Mycobacterium tuberculosis has been a co-evolving pathogen during the major phases of human evolution.[1] The historically best documented epidemic of tuberculosis, the disease caused by *M. tuberculosis,* has emerged in parallel with industrialization and urbanization some 250 years ago in the western world.[2] While it has declined for a long time in that area of the world to now very low levels, it has emerged in other parts of the world with population growth, migration, and the devastating impact of infection with the human immunodeficiency virus (HIV) over the past 30 years. Despite important recent advances in its diagnosis [3] and treatment [4], tuberculosis remains one of the leading causes of death worldwide.[5] In the year 2008, there were an estimated 9.4 million incident cases of tuberculosis, 11.1 million prevalent cases, 1.3 million deaths among non-HIV infected persons and an additional 0.52 million deaths among HIV-infected persons.[5] Despite the worldwide implementation of the World Health Organization (WHO)'s recommended DOTS Strategy, the estimated global incidence rate has peaked at 143 (95% credible range 136–151) cases per 100 000 population since 2004.[5]

The WHO reports that one-third of the world population is infected by the tubercle bacillus [6]. As this estimation cannot be verified with currently available methods, it is best an uncertain estimate of the number of persons in the world who have at one time or the other become latently infected with *M. tuberculosis*.[7] The majority of individuals with *M. tuberculosis* infection is likely to be asymptomatic, and the infecting organism could have been eliminated subsequently in a substantial proportion of them.[8] Latent infection with *M. tuberculosis* is pragmatically defined as presumptive infection with *M. tuberculosis* complex, as evidenced by a positive tuberculin skin test reaction and / or a positive interferon-γ release assay (IGRA) result without any sign of clinically or radiologically manifest disease. Direct identification of individuals who are latently infected with live *M. tuberculosis* without active disease is not possible. The term of "latent infection with *M. tuberculosis*" (often also somewhat confusingly termed "latent tuberculosis infection" abbreviated as "LTBI") is thus misleading as immunodiagnostic tests ascertain a state of persistent *M. tuberculosis*-specific immune responses rather than true latent infection with *M. tuberculosis*.[7] In this article, we pragmatically refer to individuals with latent infection with *M. tuberculosis* as those with an adaptive immune response in the form of a positive tuberculin skin test and / or *M. tuberculosis*-specific IGRA who are potentially infected with *M. tuberculosis.*

Large numbers of tuberculosis cases will continue to arise from a pool of individuals with latent infection with *M. tuberculosis* by endogenous reactivation. Indeed, with the progressive reduction in ongoing transmission and continuing aging of the worlds´ population, tuberculosis arsing from endogenous reactivation of latent infection with *M. tuberculosis* now constitutes the majority of reported tuberculosis cases in low and intermediate tuberculosis burden areas.[9]

Treatment of latent infection with *M. tuberculosis* has been started quite early subsequent to the re-discovery of the antimycobacterial activity of isoniazid in the year 1951.[10] Although the drug has been shown in randomized controlled trials to be efficacious in reducing the risk of tuberculosis among latently infected subjects with or without HIV coinfection,[11-12] long courses of treatment lasting 6 to 12 months are currently recommended. The adherence to isoniazid preventive therapy and the field effectiveness are often suboptimal. There are also concerns over adverse effects of isoniazid preventive therapy, especially hepatotoxicity.[11-12] Attempts have therefore been made to identify shorter and perhaps better tolerated drugs and regimens. Attention is naturally focused on two of the existing drugs, rifampicin and pyrazinamide, that have shown very good sterilizing activity in both animal studies

[13-14] and human trials.[15-16] Newer drugs showing good sterilizing activities in animal studies [17-22] might also be effective to prevent tuberculosis in humans.

This article will examine the existing approaches for the treatment of latent infection with *M. tuberculosis*. Where appropriate, evidence levels for the recommended treatment regimens are given in accordance with the grading system of the Scottish Intercollegiate Guidelines Network (Appendix).[23]

The latent infection state

Mycobacterium tuberculosis is able to persist within the human host for long periods without causing clinically manifest disease. Chronic persistence within the human host involves alterations of the bacillary metabolic processes with apparent arrest or slowing of multiplicative activities.[24, 25, 26, 27] Whether "dormancy" is the correct term for this state of altered metabolism has been a matter of debate. The factors and mechanisms for such altered state of metabolism are only beginning to be elucidated, and adaptive bacillary response to hypoxia within the granuloma could be one of the factors.[28] The ability of *M. tuberculosis* to enter a persistent phase carries major implications on its preventive treatment, as the current drugs are not expected to act when their target metabolic processes are switched off.

Using forms of environmental stress, like hypoxia or acid suppression, *in vitro* models have been developed, both to elucidate the underlying mechanisms of latent infection with *M. tuberculosis* and to study the action of drugs under such conditions.[28-31]. In one of such models, the Wayne model, a sealed, standing culture became progressively more hypoxic on incubation, with a concomitant shift in *M. tuberculosis* physiology.[29] Molecular signatures of such hypoxic stress responses are accumulating, but correlations with human infection / disease status are still unclear.[28, 32-34].

Models of latent infection with *M. tuberculosis* have been developed in mice, guinea pigs, zebrafishes, rabbits, and non-human primates.[28] In the Cornell model,[35] mice infected with *M. tuberculosis* are treated with isoniazid and pyrazinamide to induce a temporary "latent" state during which no detectable bacilli can be recovered by organ culture and guinea pig inoculation. This and similar kinds of models have been used extensively to study the action of drugs on latent infection with *M. tuberculosis*.[13, 14, 17, 19, 28]

Diagnostic Issues

In contrast with the various clinical manifestations [36] and high fatality of untreated tuberculosis,[37] latent infection with *M. tuberculosis* is by definition asymptomatic, and latently infected individuals do not shed bacilli into the environment and are thus non-infectious. Intervention on such latent infection state is justified primarily because of the risk of developing disease. Among young individuals with positive tuberculin skin tests identified during tuberculosis contact tracing, around 5% will develop active disease in the first five years and another 5% in the rest of their lifetime [38, 39, 40, 41]. The risk is, however, modulated by age of infection [42] and many other host factors (**Table 1**) [39, 43-46]. In a more recent study from Germany, 6 (15%) out of 41 untreated close contacts with a positive result by interferon-□ release assay (IGRA) developed active tuberculosis within 2 years following contact with an infectious index case.[47] Most of the tuberculosis cases in that study involved ethnic minorities, and only two of them were culture-confirmed. A somewhat lower proportion was observed in another study from Turkey, in which 4 (7%) out of 54 untreated children with a positive IGRA result during contact examination developed active tuberculosis after 93 person-years of follow-up [48]. IGRA did not appear to perform better than the tuberculin skin test among tuberculosis contacts in the Gambia, in which most of the tuberculosis cases were detected during the initial examination, and subsequent disease rate among subjects with a positive result for either test was much lower [49].

Table 2 summarizes the characteristics of the existing diagnostic tools for latent infection with *M. tuberculosis*. [39, 47-51] With the low bacillary load and suppressed metabolic manifestations, the diagnosis of latent infection with *M. tuberculosis* has all along depended on the detection of host response, rather than the presence / activity of the pathogen itself.[50] Immunodiagnostic methods may underperform among those who fail to mount an adequate immune response.[39, 50, 52, 53] More importantly, currently available immunodiagnostic test are unable to differentiate individuals who will subsequently develop tuberculosis from those who will not [39, 47-49]. They also fail to distinguish recent infection from remote infection that carries a much lower risk for the development of active disease.[38, 39, 50, 51] This may pose another major obstacle in areas and / or age groups with a high background prevalence of latent infection with *M. tuberculosis*.[6] Ongoing researches are focusing on antigens expressed during different metabolic phases of *M. tuberculosis* [54] and / or cytokines expressed by the human host.[55] It is hoped that they may help to improve the performance of immunodiagnostic tests in future.

Mechanisms of Drug Action

From observations in both animal and human studies, it has been postulated that a patient with tuberculosis can harbour four hypothetical populations of organisms (**Figure 1**).[24] Three major actions are proposed for the currently available antituberculosis drugs: [56]

i) bactericidal action (ability to kill actively growing bacilli rapidly), often assessed by the decrease in quantitative sputum culture bacillary count in the initial few days of treatment,[57]

ii) sterilising action (ability to kill persisters under acid inhibition or with spurts of metabolism), as reflected by the ability to prevent relapse or its proxy marker like 2-month sputum culture conversion rate,[58]

iii) prevention of emergence of bacillary resistance to drugs.

Of the currently available antituberculosis drugs, isoniazid has the highest early bactericidal effect against rapidly growing tubercle bacilli, while rifampicin and pyrazinamide are thought to have the greatest sterilizing effects against those with spurts of metabolism and under acid inhibition respectively.[56, 57]

Clinical Trials with Isoniazid

After the re-discovery of isoniazid there followed exploration of treatment with isoniazid alone and in combination with para-aminosalicylic acid or streptomycin in the treatment of tuberculosis with encouraging results.[59] Encouraging data also emerged in its use to prevent experimental tuberculosis in guinea pigs.[60] However, there were concerns over its efficacy in preventing disease or infection as well as the possible emergence of drug resistance.[10] A series of large-scale clinical trials were initiated by the United States Public Health Service (USPHS) within program settings to address this important issue. The first of these studies began in 1955 but it only examined whether the frequency of complications of primary tuberculosis could be decreased by the use of isoniazid.[61] Four subsequent randomized controlled trials were started in the 1950s and were completed in the 1960s, including a total of 27,857 household contacts [62-63], 7,333 villagers in Alaska [64] and 24,838 patients in psychiatric institutions.[65] Cluster randomization was done by household, village, or hospital ward. Isoniazid or matching placebo was given for 1 year, at a dose of 300 mg daily or 5 mg/kg for children. These studies, by their sheer sizes, helped to establish the efficacy of isoniazid in the treatment of latent infection with *M. tuberculosis*.

Follow-up data from the Alaskan study [64, 66] also suggested that the protective effect of isoniazid preventive chemotherapy persists for up to 19 years, even though the

offering of open-label treatment to all participants might have affected the accurate assessment of protective effect after 10 years. Prolonged follow-up of a cohort of children up to 30 years also supports a long-lasting protective effect.[67] It therefore appears that, among non-HIV infected subjects in areas without excessive risk of ongoing transmission, treatment of latent infection with *M. tuberculosis* produces a lasting effect.

Table 3 summarizes the results of randomized controlled trials on the treatment of latent infection with *M. tuberculosis* with a placebo / no treatment arm in non-HIV infected persons [62, 68-74]. In a meta-analysis [11] involving 73,375 subjects in 11 placebo-controlled randomized trials, treatment with isoniazid for 6 to 12 months reduced the risk of tuberculosis by 60% (risk ratio (RR):0.40; 95% confidence interval (CI): 0.31 to 0.52) over two years or longer (Grade A). Preventive therapy reduced deaths from tuberculosis, but not all-cause mortality.

No significant difference was found in the risk reduction between 6 months (RR 0.44, 95% CI 0.27 to 0.73) and 12-months (RR 0.38, 95% CI 0.28 to 0.50) of isoniazid.[11] In the International Union Against Tuberculosis (IUAT) Trial, the only study that included direct comparison between 6 and 12 months of isoniazid, a total of

28 000 persons with fibrotic pulmonary lesions compatible with tuberculosis were followed for 5 years after receiving varying durations of isoniazid at 300 mg daily given in 35-day packages for self-administered treatment.[68] On an intention to treat basis, 12 weeks, 24 weeks and 52 weeks of isoniazid reduced the risk of tuberculosis within 5 years by 21%, 65% and 75% respectively, as compared to placebo. There was no statistical difference between the effectiveness of the 24-week and 52-week regimens under the study conditions, but both of them prevented significantly more tuberculosis cases than either the 12-week regimen or placebo. Hepatitis occurred at a frequency of 0.12%, 0.25%, 0.36%, and 0.52% in the placebo, 12-week, 24-week and 52-week arms respectively. The 24-week regimen prevented more tuberculosis cases (2.6 vs 2.1 tuberculosis cases) per case of hepatitis than the 52-week regimen.

When analysis was restricted to those participants who took at least 80% of doses from each calendar package and took all calendar packages for the entire assigned duration ("completer-compliers") in the IUAT Trial, 12, 24, and 52 weeks of isoniazid reduced the risk of tuberculosis by 31%, 69% and 93% respectively (all inter-regimen P <0.05). Despite possible selection bias in secondary subgroup analyses, such results and the study among Netherlands army recruits [71] suggested considerably higher efficacies might be achievable among adherent patients than the overall effectiveness

as observed among all patients. In one of the USPHS household contact studies [63], the subsequent risk of tuberculosis was reduced by 68% and 16%, respectively, among those taking at least 80% of the recommended number of pills for at least 10 months and less than 10 months. In the Alaskan study [75, 76], the decline in the case rate became nearly horizontal at 9 to 10 months when the tuberculosis case rate was plotted against months of treatment taken. Based on these observations, Comstock inferred that 9 to 10 months of isoniazid was the optimal duration, which formed the basis for the revised current recommendation in the United States.[39] Extending treatment beyond 12 months did not appear to reduce the tuberculosis risk in the Alaskan study and the Veterans Administration Cooperation Study. [73]

The use of a daily isoniazid dosing schedule is well supported by randomized controlled trials (Grade A).[11] Twice-weekly isoniazid dosing at 15mg /kg (max 900mg) is also used in the United States to facilitate direct observation in the treatment of latent infection with *M. tuberculosis* (Grade D).[39, 77] Such dosing schedule has not been tested in randomized controlled trials among non-HIV infected persons (table 3). Its likely efficacy is extrapolated mainly from a clinical trial on active tuberculosis.[78]

In children, randomized trials are available only for the 12-month regimen. Extrapolation from adult studies may be reasonable. However, a recent study found a low peak serum concentration of isoniazid among young South African children (median age 3.2 years) given isoniazid daily at 4 to 6 mg/kg, especially among intermediate or fast acetylators.[79] and higher daily doses of 8 to 12mg/kg may be required to achieve similar isoniazid concentrations as in adults. With the high serum level to minimal inhibitory concentration ratio for isoniazid [56] and the use of isoniazid at daily dosage of 5mg / kg among young children in virtually all clinical trials [11], it remains an open question whether the higher dosage is necessary.

Isoniazid-related Hepatotoxicity

Many of the earlier trials on isoniazid were conducted before its potential hepatotoxicity was well recognized.[10] At first, the isolated reports of jaundice in the early USPHS clinical trials were not conclusively linked to isoniazid.[66] However, with the subsequent widespread use of the drug in the treatment of latent infection with *M. tuberculosis* in the United States, serum transaminase elevations and other hepatic abnormalities were soon recognized.[80] After the occurrence of 19 cases of hepatitis resulting in two deaths among 2321 contacts treated with isoniazid in an outbreak,[81] the USPHS undertook a major surveillance study among 13,838 persons in 21

participating health departments.[82] In that study, the overall frequency of isoniazid-related hepatitis was 10.3 per 1000 participants (1%), with most of them occurring within the first three months of treatment. The hepatitis risk increased sharply with age, with 0%, 0.3% 1.2% and 2.3% among those aged below 20, 20 to 34, 35 to 49 and 50 to 64 years respectively. Daily alcohol consumption was also an important risk factor. Hospitalization frequency was up to 5.0 per 1,000 treatment initiations. There were 8 fatalities with a mortality of 0.6 per 1,000 persons. It is noteworthy that of the eight deaths in the 20-city study, seven occurred in the Baltimore area which was later shown to have had an excessive increase in cirrhosis of the liver when compared with the two years earlier and later.[83]

In a meta-analysis involving 38,257 subjects treated with isoniazid in six earlier studies, clinical hepatitis ranged from 0.0 to 2.9%.[84] The combined frequency was 0.6% in absence of age adjustment. More recently, the frequency of symptomatic hepatitis has been estimated to be 1 to 3 per 1,000 persons, and much lower hospitalization (0.1 to 0.2 per 1,000 persons) and mortality (0.0 to 0.3 per 1,000 persons) have been reported.[85, 86] Such a decline might reflect more careful patient selection and active monitoring for early signs of adverse effects during treatment.[39]

Other Isoniazid-related Adverse Drug Events

The adverse drug events from isoniazid are summarized with those of other antituberculosis drugs in Table 4.[87-91] Mild and transient headache, nausea, and dizziness were reported in clinical trials of isoniazid among non-HIV infected subjects.[11] Peripheral neuropathy, related to a dose-dependent inhibitory effect of isoniazid on the function of pyridoxine metabolites, is uncommon(<0.2%) in healthy individuals. It is more frequently encountered in the chronically alcohol-dependent, malnourished persons, pregnant women and HIV-infected subjects,[87-89] but it can be prevented as well as treated by pyridoxine. It is not generally held that pyridoxine should be given routinely [92], but it should be prescribed to patients at risk of such complication, including those with underlying nutritional deficiency or higher requirements, and in persons in whom peripheral neuropathy may develop as a result of the underlying condition, thus leading to confusion over the cause. Central nervous system reactions, such as convulsions, encephalopathy, optic neuritis, memory impairment, and psychosis, are rare at normal doses. Antinuclear antibody is more common than the actual lupus-like syndrome.

HIV-infected Individuals

In a study by Selwyn *et al*. in United States, the risk of tuberculosis among tuberculin skin test-positive and HIV-infected subjects was at least 7.9 cases per 100 person-years.[93] The risk of developing tuberculosis increases with the degree of immunosuppression,[94] and remains elevated (though at a reduced level) even after the initiation of anti-retroviral therapy.[95] Tuberculin skin testing remains a useful primary screening test for the diagnosis of latent infection with *M. tuberculosis* among HIV-infected persons despite possible limitations in sensitivity[96], with 24-fold difference in risk between test-positive and test-negative subject in the above quoted study.[93] Data on the disease-predicting values of IGRA among HIV-infected persons are still scanty.[97]

Table 5 summarizes the results of randomized controlled trials on the treatment of latent infection with *M. tuberculosis* with a placebo / no treatment arm among HIV-infected persons.[98-107] In a randomized controlled trial among HIV-infected subjects in Haiti [98], a 12-month course of isoniazid reduced the incidence rate of tuberculosis from 7.5 to 2.2 per 100 person-years (RR:0.29, CI 0.09-0.91) among HIV-infected subjects. In subgroup analysis, there was significant reduction (RR 0.22, 95%CI: 0.05 -1.00) among tuberculin skin test-positive subjects (cut-off >=5mm) but not among tuberculin skin test-negative subjects (RR 0.70, 0.15-3.28). In this particular

study, isoniazid treatment also delayed progression to HIV-associated morbidity including AIDS and death. In a Ugandan trial,[99] 6 months of isoniazid significantly reduced tuberculosis risk among tuberculin skin test-positive subjects (RR: 0.33, 95% CI:0.14-0.77) but not subjects with anergy (RR: 0.83, 95% CI: 0.34 - 2.04). Survival did not differ between the study arms, but anergic subjects had a higher fatality than those with a positive tuberculin skin test. In a follow-up analysis, benefit in tuberculin skin test-positive persons was lost after the first year.[100] No significant protective efficacy was observed for 6 months of isoniazid among HIV-infected subjects after a median follow-up of 1.83 years in Kenya, but the small number of tuberculin skin test-positive subjects (67-69 per arm) might not have provided adequate power to pick up any difference.[101]

In a randomized controlled trial among HIV-infected subjects with anergy in the United States, tuberculosis was diagnosed in only 6 of 257 patients in the placebo group and 3 of 260 patients in the isoniazid group after a mean follow-up of 33 months.[102] As the incidence of tuberculosis was low, it does not support the use of isoniazid treatment in anergic HIV-infected subjects in absence of recent exposure to a case with bacteriologically confirmed tuberculosis of the respiratory tract. There were also no

significant differences between the two groups with regard to death, death or the progression of HIV disease, or adverse events.

Only a single randomized controlled trial in Zambia tested 6 months of isoniazid twice a week against placebo among HIV-infected persons.[103] However, only combined analysis of treatment with either 6 months of isoniazid or 3 months of rifampicin plus pyrazinamide against placebo reached statistical significance (RR: 0.60, 95% CI: 0.40-0.89). The effect of preventive therapy also declined after the first year of the study. By 18 months the rates of tuberculosis in the treated groups were similar to that in the placebo group, even though the cumulative risk of tuberculosis remained significantly lower within the first 2.5 years.[104]

Among 4316 HIV-infected subjects in 7 trials (98-106) included in a recent meta-analysis,[10] treatment with either 6 or 12 months of isoniazid was associated with a significantly lower incidence of tuberculosis (RR: 0.67, 95% CI:0.51-0.87). This benefit was more pronounced in individuals with a positive tuberculin skin test (RR: 0.36, 95% CI: 0.22 to 0.61) (Grade A), but failed to achieve statistical significance among those who had a negative tuberculin skin test (RR: 0.86, 95% CI: 0.59 - 1.26) (insufficient evidence). Overall, adverse events leading to stopping treatment occurred

in 2.8% of those receiving isoniazid as compared to 1.8% of the placebo arm (RR: 1.66, 95%CI:1.09 - 2.51). The reduction in mortality just reached statistical significance among individuals with a positive tuberculin skin test (RR: 0.74, 95% CI: 0.55 to 1.00). Despite the delay in HIV progression that was observed with isoniazid treatment in the Haiti trial,[98] confirmation of such effect awaits further trials. It is not possible to determine whether the effects of treatment are influenced by the HIV/AIDS progression stages. The optimal duration of isoniazid for the prevention of tuberculosis in HIV-seropositive individuals is also unclear. Both a 6-month regimen [85-87, 89] and a 12-month regimen [98] are effective (Grade A), but none of the trials directly compared isoniazid regimens of different durations. Given the uncertainty, the American Thoracic Society discourages the use of a 6-month isoniazid regimen for patients with HIV infection. [39]

From the only two available studies with long-term follow-up data [100, 104], the protection of isoniazid treatment in HIV-infected persons appears to be short-lasting (1 - 2.5 years). As both of these studies were conducted in areas with a high incidence of tuberculosis, re-infection after completion of isoniazid preventive therapy could have been an important factor, taking into account the heightened risk of rapid progression to disease among HIV-infected subjects.

Alternative Short-Course Regimens

The long duration required for the treatment of latent infection with *M. tuberculosis* triggered a series of clinical trials in search for a "short-course" regimen. Attention was naturally directed to those drugs with putative sterilizing capacity against persisters,[13, 14, 56] especially rifampicin and pyrazinamide, the pivotal agents that successfully shortened the treatment duration for tuberculosis in human trials.[15, 16]

In an animal experiment, a non-replicating bacillary population of limited size was developed in mice vaccinated with BCG vaccine to mimic latent infection with *M. tuberculosis*.[13] After treatment with 6 months of isoniazid, 3 months of rifampicin, 2 months of rifampicin plus pyrazinamide, and 2 months of rifampicin plus pyrazinamide plus isoniazid, the proportions of mice with positive spleen cultures for *M. tuberculosis* were 100%, 20%, 0%, and 80% respectively. The 2-month regimen of rifampicin plus pyrazinamide appeared to show the best treatment-shortening potential, and addition of isoniazid showed an antagonistic effect. These results were very encouraging even though there could be pitfalls in extrapolating experimental observations from a murine model to man.[28, 108]

In the 1990s, effective regimens were already fully established for the treatment of both latent infection with *M. tuberculosis* [62-74] and tuberculosis.[15, 16] Under such a situation, there would be ethical and logistic difficulties in assigning a huge number of subjects to experimental preventive regimens in a way similar to what was done in the 1950s.[62-65] Most of the explorative trials on alternative regimens were therefore done among groups with a very high risk for tuberculosis, like silicosis patients [73] or HIV-infected subjects, to reduce the sample size and follow-up time. Only some of them contained a placebo / no treatment arm (**Tables 3 and 5**), as it would be acceptable to compare a new regimen with the standard regimen of isoniazid for 6 or 12 months.[109-110] **Table 6** summarizes the comparison of efficacy between isoniazid and the alternative regimens, while **Tables 7 and 8** summarize the adverse events leading to termination of treatment in those randomized controlled trials for latent infection with *M. tuberculosis* conducted in or after the 1990s.

Rifampicin plus Pyrazinamide

In the year 2000, a multinational trial reported that 2 months of rifampicin and pyrazinamide was as effective as 12 months of isoniazid in reducing tuberculosis in HIV-infected individuals with latent infection with *M. tuberculosis* (**Table 6**).[111]

Drug discontinuation was significantly higher in the rifampicin plus pyrazinamide arm than the isoniazid arm (**Table 8**). However, lower number of patients in the rifampicin plus pyrazinamide arm had abnormal liver function test results that were grade 4 or resulted in study drug discontinuation (11/791 vs 28/792, P = 0.02). Treatment completion was also higher for rifampicin plus pyrazinamide arm than the isoniazid arm (80% vs 69%, P<0.001).

In a meta-analysis of different regimens for latent infection with *M. tuberculosis* among HIV-infected subjects,[12] combined analysis of 428 subjects on rifampicin plus pyrazinamide for 2 to 3 months and 428 subjects on placebo in 2 trials [103, 106] the combined relative risk of tuberculosis was 0.54 (95% CI: 0.34 - 0.86) for rifampicin plus pyrazinamide vs. placebo, even though treatment was more likely to be stopped because of adverse drug events (RR: 7.84, 95% CI: 2.60 - 23.67). Equivalent efficacy (RR: 1.03, 95% CI: 0.75 - 1.40) was found between isoniazid (6 or 12 months) and rifampicin plus pyrazinamide among a total of 3409 subjects in 5 randomized clinical trials in the same meta-analysis (**Table 6**).[103, 106, 111-113] However, the isoniazid regimen was less likely to be stopped because of adverse events (RR: 0.63, 95% CI 0.48 to 0.84). Partly because of this, the proportion of patients completing treatment was higher for the shorter RZ regimen in only two studies.[111, 113] On the other hand,

hepatotoxicity did not appear to be a prominent feature for the use of rifampicin plus pyrazinamide among HIV-infected subjects.[12] Re-analysis of the data in the trial published by Gordin *et al*. in 2000 also confirmed the absence of excess hepatotoxicity risk with the combination of rifampicin plus pyrazinamide in HIV-infected individuals.[114]

In another trial among HIV-infected subjects, 3 months of isoniazid plus rifampicin and pyrazinamide was equivalent to 6 months of isoniazid monotherapy and significantly reduced the risk of tuberculosis as compared to placebo.[109] However, treatment was much more likely to be stopped because of adverse events in comparison with either placebo or isoniazid (**Tables 7 and 8**).

With the reported efficacy of a 2-month course of rifampicin and pyrazinamide in the treatment of latent infection with *M. tuberculosis* among the HIV-infected individuals,[111] the American Thoracic Society and Centers for Disease Control and Prevention (CDC) issued a joint statement in 2000 entitled "Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection".[39] Emphasis was put on directing tuberculin testing to populations at risk of developing tuberculosis, as well as more treatment options including short-course rifampicin-based regimens. As the

drugs involved had been used extensively in the treatment of tuberculosis, there was apparently not too much concern over adverse effects. In fact, to promote better acceptance, there was call for simplified monitoring that emphasizes clinical evaluation more than laboratory examination. Soon after such recommendations, reports of severe drug-induced liver injury including deaths followed widespread use of rifampicin plus pyrazinamide [115,116]. These reports prompted revision of the guidelines in August 2001 to reduce the dose of pyrazinamide (to 20mg / kg or below) and ensure closer monitoring.[116] In a national survey of 8,087 patients given rifampicin plus pyrazinamide in the United States, the frequencies of asymptomatic elevation of aspartate aminotransferase more than 5 times upper limit of normal) and clinical hepatitis were 25.6 (95% CI: 22.3-29.3) and 18.7 (95% CI: 15.9-21.9) per 1,000 therapy initiations, respectively, with 23 (2.8 per 1,000) hospitalizations and 7 (0.9 per 1,000) fatalities.[117] Increasing age, an abnormal baseline aspartate aminotransferase level (often associated with alcohol use), and unemployment within the past 24 months were found to be independent risk factors for hepatotoxicity in a cohort study on the use of 2 months of rifampicin plus pyrazinamide among jail inmates and homeless persons.[118] Such events could occur at a low pyrazinamide dose, despite biochemical monitoring and at the end of therapy.[119] Many of these required hospitalization and some required liver

transplantation.[119, 120] Fatality was associated with higher age or use of other medications.[119]

In three clinical trials involving randomized or systemic allocation of non-HIV infected subjects, 7.7%, 35%, and 10% of those in the 2-month rifampicin plus pyrazinamide arms developed significant hepatotoxicity with aspartate or alanine aminotransferase in excess of 5 times the upper normal limit.[121-123] All of these proportions were significantly higher than those observed in the corresponding isoniazid arms. For unknown reasons, the frequency of hepatotoxicity in the use of rifampicin plus pyrazinamide in the treatment of latent infection with *M. tuberculosis* among non-HIV infected subjects appeared to be higher than those reported in the historical short-course trials (involving concomitant use of isoniazid, rifampicin and pyrazinamide) in the treatment of active tuberculosis. [15, 16]

A high frequency of hepatitis of 11% to 14% was initially reported in early studies using high dosages of pyrazinamide (40-70mg / kg daily) in combination with isoniazid [124]. With the adoption of lower drug dosages, 2% to 5% of patients developed hepatitis attributable to pyrazinamide while they were put on the

standard short-course regimens for treatment of tuberculosis [15, 16, 125, 126]. In the Hong Kong study,[122] the reported hepatotoxicity frequency of 35% with 2 months of rifampicin plus pyrazinamide (daily dosage largely below 20 mg/kg) was much higher than that observed among patients with silico-tuberculosis put on a 8-month regimen of streptomycin, isoniazid, rifampicin and pyrazinamide (daily dosage 30 mg/kg).[127] In a retrospective cohort study in the Netherlands, preventive treatment with rifampicin plus pyrazinamide caused severe hepatotoxicity more often than preventive treatment with isoniazid (OR: 2.61, 95% CI: 1.26-5.39) and triple- or quadruple-drug regimens for tuberculosis (OR: 2.61, 95% CI: 1.21-5.59).[128] As the substitution of isoniazid by moxifloxcin has not been reported to increase the frequency of hepatotoxicity in a tuberculosis treatment trial [129], intrinsic differences of host status between latent infection with *M. tuberculosis* and tuberculosis might account partly for the difference in hepatotoxicity, in line with the apparent absence of excess hepatotoxicity of rifampicin plus pyrazinamide among HIV-infected subjects [12, 111]. In this regard, treatment for latent infection with *M. tuberculosis* was also terminated because of hepatotoxicity in six out of 12 consecutive African contacts of multidrug-resistant tuberculosis given pyrazinamide and ethambutol.[130]

None of the randomized controlled trials among non-HIV infected are adequately powered to provide a conclusive answer on efficacy.[121-123]. However, drug-induced liver injury is much less acceptable for preventive therapy among persons who run a 10% lifetime risk of developing tuberculosis than among persons with a potentially fatal disease if left untreated. The revised ATS/CDC recommendations now state that rifampicin plus pyrazinamide should generally not be offered to persons with latent infection with *M. tuberculosis*.[86]

Rifampicin Monotherapy

Rifampicin at a dose of 10mg / kg daily (maximum 600mg) for 4 months is currently an acceptable alternative regimen for treatment of latent infection with *M. tuberculosis* (Grade B).[39] Only a single randomized clinical trial assessed the efficacy of rifampicin monotherapy.[73] In this study, isoniazid for 6 months, rifampicin for 3 months and isoniazid plus rifampicin for 3 months were compared against placebo. Pulmonary tuberculosis was observed in 13% of the three treatment groups combined as compared to 27% of the placebo group within 5 years ($p<0.01$). In the 389 patients who were followed up to 5 years, the 3-month rifampicin regimen significantly reduced the risk of tuberculosis as compared to placebo (**Table 3**). No significant difference in efficacy was observed between the isoniazid and the

rifampicin arm (**Table 6**) and acquired drug-resistance did not appear to be a problem with either regimen. The rifampicin-alone therapy was very well tolerated, with serious adverse effects occurring with similar frequency as in the placebo arm (**Table 7**). None of the 172 silicosis patients in the rifampicin arm developed hepatitis. Low frequencies of serious adverse events and high proportions of treatment completion were similarly demonstrated in later cohort studies.[131-135] In two recent randomized controlled trials among predominantly non-HIV infected individuals,[136-137] a significantly higher proportion completed treatment with 4 months of rifampicin than with 9 months of isoniazid. Adverse events leading to termination of treatment also appeared to be fewer in the rifampicin arm in both studies (**Table 8**). In the larger study, grade 3 or 4 hepatotoxicity occurred in 16 of 422 (3.8%) isoniazid recipients as compared to 3 of 418 (0.7%) rifampicin recipients.[137] No randomized controlled trial has been published on the use of rifampicin alone in predominantly HIV-infected persons, perhaps because of concern over the possibility and consequence of acquired rifampicin resistance. In a meta-analysis involving a total of 3586 subjects [138], non-completion was 8.6% to 28.4% among patients who received 4-month rifampicin therapy and 24.1% to 47.4% among patients who received 9-month isoniazid therapy (RR, 0.53; 95% CI, 0.44-0.63). Grade 3 or 4 hepatotoxicity leading to drug discontinuation was also significantly lower (0% to 0.7% vs 1.4% to 5.2%, RR: 0.12, 95% CI, 0.05-0.30). A large scale multicentre

trial is now underway to assess the effectiveness of 4 months rifampicin [139]. The optimal duration of rifampicin remains uncertain. Although 3 months of rifampicin only reduced the risk of tuberculosis by 52% among silicosis patients,[73] tuberculosis incidence was actually the lowest in that arm. The high residual risk could well reflect the underlying host status, rather than treatment efficacy.

Isoniazid plus Rifampicin

A 3-month regimen of isoniazid plus rifampicin has also been recommended as an alternative for the treatment of latent infection with *M. tuberculosis* by the British Thoracic Society (Grade A).[140]. Its efficacy and adverse events leading to treatment termination were not significantly different from those of 6 months of isoniazid (**Tables 6 and 7**). Hepatic adverse reactions (mainly elevated transaminases) also occurred at similar frequency (3 cases in both arms). Additional hepatotoxicity was however shown by a meta-analysis of patients put on the combined regimen from different kinds of studies.[84] No hepatitis case was reported among 556 HIV-infected subjects in the 3-month isoniazid plus rifampicin arm in the Uganda trial.[99] In the recent Cochrane analysis among HIV-infected subjects,[12] isoniazid plus rifampicin significantly reduced the risk of tuberculosis (RR: 0.41, 95% CI: 0.21 to 0.81) and death (RR: 0.69, 95% CI: 0.50 to 0.95) as compared to placebo among 1179 subjects in two trials, but

there was a higher incidence of adverse events leading to termination of treatment (RR 16.72, 95% CI: 3.29, 84.89). Equivalent efficacy (RR: 0.97, 95% CI 0.52 to 1.83) was observed between isoniazid (for 6 to 12 months) and isoniazid plus rifampicin (for 3 months) among 1601 subjects in 4 trials. Adverse events leading to treatment termination were somewhat less frequent in the arm receiving isoniazid monotherapy (RR: 0.79; 95% CI; 0.50, 1.23), but the difference was not statistically significant. Very similar conclusions on relative efficacy and safety of the two regimens were made in another meta-analysis of all the 5 trials from both HIV-infected and non-HIV infected subjects.[141] In a study among children, no clinical disease or adverse event leading to treatment termination was observed in 232 patients on 9 months of isoniazid and 238 patients on 4 months of isoniazid plus rifampicin, but patients who received isoniazid monotherapy were significantly less compliant.[142] Martinez *et al.* also reported better adherence with 3 months of isoniazid plus rifampicin as compared to 12 months of isoniazid.[143] However, in two other studies, the proportions completing were similar between 3 months of isoniazid plus rifampicin and 6 months of isoniazid.[99,113] An observational study among First Nations Canadians in Saskatchewan reported much higher completion (80% vs 19%) for 6 months of twice weekly isoniazid plus rifampicin than for 12 months of daily, self-administered

isoniazid.[144] The use of direct treatment observation in a special population could be a contributing factor.

Isoniazid plus rifapentine

Rifapentine, a long-acting rifamycin, has been shown to have good activity in treatment of latent infection with *M. tuberculosis* in the mouse model, when used together with isoniazid in highly intermittent regimens.[145, 146] The combination of rifapentine 900 mg and isoniazid 900 mg once weekly for 12 weeks was found to be well tolerated in a recent human trial, with 2 out of 206 (1%) treated contacts showing grade 3 or 4 hepatotoxicity [147]. No conclusion can be drawn on the efficacy as the comparison was made with daily rifampicin plus pyrazinamide and the number of tuberculosis cases was very low in either arm. Close to 9000 subjects have been recruited in a large scale trial comparing 3 months of weekly isoniazid plus rifapentine with 9 months of isoniazid,[148] and the results might help to establish this highly intermittent regimen for use under direct observation in the coming two years.

Drug interactions

Most of the clinically significant interactions involving drugs metabolized by the cytochrome P450 (CYP450) system are pharmacokinetic in nature.[149-150]

Rifampicin is a powerful enzyme inducer of CYP450 and may therefore reduce serum concentration of oral contraceptives, corticosteroids, anticoagulants, anticonvulsants, anti-infectives (including antiretrovirals), cardiovasculo-therapeutics, immunosuppressants, psychotropics, sulphonylureas, theophylline and other drugs metabolized by the same pathway[151]. As rifampicin features prominently in most of the alternative treatment options of tuberculosis preventive therapy, extra caution is called for in HIV-infected individuals [152] or among older people at higher risk of drug-drug interactions. [149] Other rifamycins, like rifapentine, might also share similar enzyme-inducing activity to varying degrees. Rifabutin, a rifamycin compound with less enzyme-inducing activity, is sometimes used in the treatment of tuberculosis in HIV-infected patients together with selected protease inhibitors or non-nucleoside reverse transcriptase inhibitors. However dose modifications may be necessary. [153]

Risk of Acquiring Drug Resistance

Mutants resistant to antituberculosis drugs are known to emerge spontaneously through alterations of chromosomal genes.[154] For isoniazid, such mutants are thought to arise in 1 in 10^7 to 10^9 cell divisions, resulting in 1 effectively resistant *M. tuberculosis* bacillus in 10^6 of the bacillary population. For rifampicin, the corresponding figures are 1 in 10^{10} cell divisions, and 1 in 10^8 of the bacillary populations. With a

bacillary load of 10^8 to 10^9 in a tuberculosis patient with cavitary lung lesions, combination therapy is required to prevent the selection of resistant mutants. However, while such calculations might be algebraically sound, clinical practice shows that resistance emerges against isoniazid in 0.5%, 2.0%, and 4.0% if the companion drug is rifampicin, streptomycin, or ethambutol respectively, substantially higher than those suggested by simple product rule.[155]

The propensity for emergence of resistance might be less with the much lower bacillary load as is the case with latent infection with *M. tuberculosis*. In a systematic review [156] of 13 studies published since 1951, a total of 31 isoniazid-resistant isolates were obtained from the isoniazid groups and 24 from placebo / no treatment groups, giving a summary relative risk of 1.45 (95% CI 0.85–2.47) in the emergence of bacillary resistance during isoniazid preventive therapy. Results were similar when studies of non-HIV infected and HIV-infected persons were considered separately. However, with the small numbers and incomplete testing of isolates, it is not possible to exclude a modest increase in risk entirely.

From a theoretical perspective, selection of rifampicin-resistant mutants may be less likely to occur than selection of isoniazid-resistant mutants because of the 1 to 3 order lower spontaneous mutation rate.[154] However, rifamycin mono-resistance had emerged in 4 of 5 patients with a relapse among 31 HIV-infected patients treated once weekly with isoniazid plus rifapentine in the continuation phase of treatment against tuberculosis [157]. It therefore appears that the putative low bacillary load after the end of the intensive phase of treatment is not a sufficient condition, at least not among HIV-infected patients, to prevent the emergence of resistance to a rifamycin. There is also some evidence that a higher serum level of isoniazid did appear to play a role in the prevention of rifamycin mono-resistance in the same study.[158] A number of trials have confirmed the efficacy of 3 months of isoniazid plus rifampicin (**Tables 3, 4, and 6**), even though adding isoniazid to rifampicin is likely to increase the risk of adverse drug events, drug-induced liver injury in particular (**Table 8**). With the concern over emergence of rifampicin resistance, there could be a point of using isoniazid plus rifampicin, especially in HIV-infected patients. However, in the only trial that directly compared 3 months of rifampicin with 3 months of isoniazid plus rifampicin,[73] a smaller number of tuberculosis cases occurred in the rifampicin arm, even though the difference fell short of statistical significance. In the mouse study by Lecoeur et al,[13] isoniazid also appeared to antagonize the sterilizing activity of

rifampicin plus pyrazinamide. Resolution of this dilemma will have to await further studies.

Contacts of patients with drug-resistant tuberculosis

In an observational study among 2,795 tuberculin-positive Southeast Asian refugees prescribed isoniazid preventive therapy at the time of their resettlement in United States [159], 19 cases of tuberculosis were detected during follow-up. Fifteen of them were culture positive, with 8 of isolates being isoniazid-susceptible and 7 isoniazid-resistant. A case-control analysis showed that taking isoniazid for 3 months or less was associated with a 6-fold increase in risk (as compared to longer treatment) for subsequent isoniazid-susceptible tuberculosis, but there was no excess risk for subsequent isoniazid-resistant disease. In another observational study among 204 tuberculin skin test converters in an outbreak of isoniazid- and streptomycin-resistant tuberculosis among Boston's homeless population,[131] 6 of 71 (8.6%) individuals who received no preventive chemotherapy, 3 of 38 (7.9%) in the isoniazid group, and none of the 86 in the rifampicin or rifampicin plus isoniazid groups developed tuberculosis. These observational studies provide evidence for the obvious assumption that isoniazid monotherapy is ineffective in reducing the risk of tuberculosis due to isoniazid-resistant *M. tuberculosis*.

In a systematic review of treatment for latent infection with *M. tuberculosis* in persons at risk for multidrug-resistant tuberculosis, only two cohort studies met the inclusion criteria.[161] The earlier retrospective cohort study found isoniazid not to be effective (RR: 0.46, 95%CI:0.07-2.32),[162] while a later prospective cohort study found individualised tailored treatment with high dose isoniazid (15–20 mg/kg/d), pyrazinamide, ethionamide and/or ethambutol and/or ofloxacin to be effective (RR: 0.20, 95%CI: 0.04-0.94).[163]

In absence of sufficient data, existing recommendations are subjective and are necessarily based largely on expert opinions, rather than on clinical evidence. Rifampicin for 4 months is a rational regimen choice for the treatment of contacts infected after exposure to a source case with isoniazid-resistant tuberculosis (Grade D).[39] Opinions differ on the management of contacts of patients with multidrug-resistant tuberculosis. On the basis of the currently available evidence, the WHO does not recommend second-line drugs for preventive therapy among contacts putatively infected with multidrug-resistant bacilli.[164] Careful clinical follow-up for at least 2 years is recommended instead. If multidrug-resistant tuberculosis is diagnosed, treatment should be started promptly with an appropriate treatment regimen.

In contrast to the WHO, CDC recommends 6 to 12 months of preventive therapy with at least two antituberculosis drugs (e.g. ethambutol and pyrazinamide or pyrazinamide and a fluoroquinolone, depending on the drug susceptibility profile of the source case's isolate) for persons likely to be infected with multidrug-resistant bacilli, especially for those thought or known to be at a high risk of progression to tuberculosis (Grade D).[165] However, high frequencies of treatment termination because of adverse events were reported for pyrazinamide-containing regimens (pyrazinamide plus ethambutol or pyrazinamide plus levofloxacin /ofloxacin).[130, 166-168] Hepatotoxicity was a prominent feature in some of these studies [130, 168]. Fluoroquinolones have been found to be generally well tolerated in the treatment of tuberculosis or multidrug-resistant tuberculosis.[129, 169] A question naturally arises as to the role of fluoroquinolone monotherapy in such situation. However, fluoroquinolones, in combination with second-line injectable drugs, currently play an important role in the treatment of multidrug-resistant tuberculosis.[169, 170] In a recent study, exposure to fluoroquinolones for more than 10 days, particularly more than 60 days before tuberculosis diagnosis, was associated with a high risk of fluoroquinolone-resistant tuberculosis.[171] Caution must therefore be exercised towards the use of fluoroquinolone monotherapy, and active surveillance remains a possible option among

contacts of cases with multidrug-resistant tuberculosis, especially those at lower risk of developing clinical disease.

Development of new drugs

Clinical trials on new drugs for treatment of latent infection with *M. tuberculosis* generally lag behind those for treatment of active tuberculosis, mainly because of the logistical difficulties associated with studies in the treatment of latent infection with *M. tuberculosis*.[172] As mentioned in a previous section, weekly rifapentine (plus isoniazid) is being explored in the treatment of latent infection with *M. tuberculosis* [148] after two randomized controlled trials on the treatment of tuberculosis [173, 174].

Adenosine triphosphate (ATP) synthesis is essential in the metabolism of mycobacteria [175, 176]. TMC207 is a novel diarylquinoline with unique activity on the mycobacterial ATP-synthase [177]. In a murine model of tuberculosis, the bactericidal effect of TMC207 was modest during the first week of treatment but increased in the following three weeks [178]. TMC207 also showed good sterilizing activity in mice. In combination with pyrazinamide, TMC207 led to bacillary sterilization in two months.[179] In another mouse study on tuberculosis, TMC207 plus rifapentine plus pyrazinamide given once weekly was more active than the current

standard regimen of rifampicin plus isoniazid plus pyrazinamide given five times per week.[180] In an early bactericidal activity study, significant bactericidal activity of TMC207(400 mg) was observed from day 4 onward in a magnitude similar to that of isoniazid and rifampicin.[181] In a phase II clinical trial, the addition of TMC207 to standard therapy for multidrug-resistant tuberculosis reduced the time to culture conversion and greatly increased the proportion with culture conversion (48% vs. 9%) at two months.[182].

As diarylquinolines are claimed to also have bactericidal activity against non-replicating mycobacteria,[165] [166] TMC207 could be a potential candidate drug for the treatment of individuals with latent infection with *M. tuberculosis*, including contacts of patients with multidrug-resistant tuberculosis.

Issues beyond Efficacy

As latent infection with *M. tuberculosis* is both asymptomatic and non-infectious, the primary target of intervention is to reduce the risk of progression to tuberculosis. However, on average, only a minority of latently infected individuals will develop disease in their lifetime.[38-42, 47-49] This necessarily sets a ceiling to the maximum effectiveness of treatment for latent infection with *M. tuberculosis* in terms of the

number of patients to be treated to prevent an active case of tuberculosis.**Figure 2** plots the number needed to treat to prevent one case of tuberculosis against the incidence of disease among the target group at different assumptions of treatment efficacies. Under all scenarios, the incidence of disease is the prime determinant of this measure of effectiveness. This would justify targeting only those at a high risk of developing tuberculosis, even at the expense of decreasing population coverage and limiting the overall impact.

Actual field practices vary widely across the world. In North America, a fairly wide range of target groups are included for screening and treatment of latent infection with *M. tuberculosis*, e.g. recent contacts, institutional clients, health care workers, immigrants from high incidence areas, persons with currently inactive fibrotic lesions, HIV-infected persons and other immunocompromised states, including those on immunosuppressive treatment.[39, 183] The WHO mainly focused on HIV-infected persons and young household contacts of patients with infectious pulmonary tuberculosis [164, 184]. Nine months of isoniazid is now recommended in United States [39] and Canada [184], while 6 months of isoniazid is still more frequently used in other parts of the world [164, 185]. Rifampicin for 4 months is an acceptable alternative regimen in United States and Canada, [33, 183] while a combination of

isoniazid and rifampicin may be used more often in United Kingdom.[186] Many factors could have entered into the strategic formulations in addition to the simple question of efficacy. With the wide variations in socioeconomic and epidemiological conditions globally, it would be necessary for each locality to set its own priority after taking into account of available scientific data and local circumstances.

Safety and Monitoring

The adverse effects of current treatment regimens also constitute a major hurdle both among HIV-infected and non-HIV infected individuals (**Tables 7 and 8**). For preventive therapy, every individual put on treatment will be subject to the potential risk of drug toxicity, but only those who would otherwise develop disease benefit from such treatment. **Figure 3** shows the impact of hepatitis and disease incidence on benefit versus risk ratio in terms of number of tuberculosis cases prevented per case of hepatitis, which readily falls below 1 when the frequency of drug-induced liver injury is high and / or the tuberculosis incidence is low. This explains why there must generally be a much lower threshold of accepting adverse drug events during the treatment of latent infection with *M. tuberculosis* than is the case with treatment of tuberculosis.

The presence of a substantial risk in latent infection with *M. tuberculosis* treatment also implies a need for careful screening and close monitoring, which may add further costs and barriers of access to care. Besides patient education and clinical monitoring, baseline and monthly (or biweekly) laboratory testing of liver enzymes is recommended for chronic alcohol users, HIV-infected persons, women during pregnancy and within three months after delivery, and those with chronic liver disease, or taking concomitant medications that can be hepatotoxic [39, 86]. Transient transaminase elevations are common and may reflect the process of hepatic adaptation [187]. However, isoniazid and / or rifampicin should be withheld as recommended if the serum transaminase level is higher than 3 times the upper limit of normal in a symptomatic patient or 5 times the upper limit of normal in the absence of symptoms [39, 188]. With the lower degree of tolerance for risk in the treatment of latent infection with *M. tuberculosis*, re-introduction of drug is seldom attempted after significant hepatotoxicity. [86]

Acceptance

Even in North America, there appears to be suboptimal acceptance of preventive therapy regimens among both clinicians and patients. Treatment of latent infection with *M. tuberculosis* was not recommended by the attending doctors in 20-30% of patients who appeared otherwise eligible in some studies.[189, 190] Physicians' reluctance to

prescribe is especially noticeable among the older individuals, possibly related to the higher incidence of drug-induced hepatitis in the elderly [82]. Even if treatment is offered, it might be refused by considerable proportions of persons [189, 191, 192]. In a retrospective survey of public and private clinics in the United States and Canada, 123 (17.1%) of 720 subjects tuberculin skin-tested and offered treatment in the same clinics declined treatment. Interestingly there was a higher likelihood for health care workers than for other tuberculosis contacts to decline [191]. In another study among health care workers at an urban teaching hospital in United States [192], only 69% of eligible persons accepted treatment against latent infection with *M. tuberculosis*. These results suggested that lack of knowledge about the treatment might not be a major factor for poor acceptance.

Adherence

In a systematic review of 78 studies in the US and Canada on adherence to treatment of latent infection with *M. tuberculosis*, treatment completion varied widely (from 19% to 96%) but was mostly suboptimal across high-risk groups, regardless of regimen [193]. Lesser variations were observed in some of the large-scale studies in public programs involving clients with similar characteristics. For example, 64% of treatment completion was reported in two large-scale retrospective reviews of medical

records (involving 9018 and 3048 contacts) of individuals who were being treated with isoniazid in contact investigation programs [189, 194] and in a 7-year prospective survey of hepatotoxicity associated with isoniazid preventive therapy (involving 11,141 patients) in a public health tuberculosis clinic [85]. A similar proportion of treatment completion (61%) was reported in a retrospective medical record review involving 19,582 treated inmates in 49 correctional facilities in the United States [195].

Similarly, treatment completion was found to be 53% in 68 public and private clinics included in a recent retrospective survey in the United States and Canada [191]. In that particular survey, a 9-month isoniazid regimen, residence in a congregate setting (nursing home, shelter, or jail), injection drug use, age above 15 years and employment at a health care facility were significantly associated with failure to complete treatment. However, associations between adherence and patient factors, clinic facilities or treatment characteristics were inconsistent across other studies [193]. Adherence is a composite behavioural endpoint. Heterogeneity in social context, provider arrangement and client profile could well have accounted for these variations. While there are suggestions that shorter durations of treatment may improve treatment completion, the higher frequency of adverse events leading to treatment termination for some of the

short-course regimens might nullify such effects, especially for rifampicin plus pyrazinamide, and possibly isoniazid plus rifampicin.[12]

Cost-effectiveness

A number of economic analyses have been conducted on the effectiveness of the treatment of latent infection with *M. tuberculosis* [196-205]. Most of them were performed under a number of epidemiological, health care utilization and costing assumptions and might not be applicable outside the specific economic realities of industrialized countries for which they were modelled. Under such assumptions, the use of isoniazid in the treatment of latent infection with *M. tuberculosis* has been found consistently to be cost-effective and often cost-saving in populations that are younger, and/or at greater risk to progress from disease. However, not all of them have taken a full account of the direct or indirect screening costs [196, 197]. Most of them based the analysis on highly defined target groups, especially recent tuberculin skin test converters [196, 198] or tuberculin skin test-positive close contacts in low tuberculosis incidence settings [196-197]. While these defined target groups might be more easily accessible and have a higher screening yield, high disease incidence, fewer adverse effects, and lower monitoring cost, they might account only for a relatively small proportion of all the tuberculosis cases within a community. Among older tuberculin skin test reactors, the

conclusions were either small positive health effects at a cost considered acceptable in developed economies [196], or in an opposite direction [199]. As it is not always easy to delineate science clearly from assumptions or value judgements in some of these modelling exercises[206], the findings might have to be taken with a grain of salt.

In a more recent cost-benefit analysis that included both screening and treatment for latent infection with *M. tuberculosis* in Germany,[200] cost of screening and treatment based on a positive result in a QuantiFERON® TB Gold In-Tube (QFT) test alone amounted to Euro 215.79 per close contact, less than that of dual step-testing (Euro 227.89) or using the tuberculin skin test alone (Euro 232.58). The cost-effectiveness of QFT-based procedures were sensitive to low treatment completion or increasing price, but the relationship between the strategies remained robust when the disease-predicting power of QFT was lowered to that for the tuberculin skin test in a sensitivity analysis. It therefore appears that the potentially higher specificity of QFT may help to improve cost-effectiveness of targeted screening of latent infection with *M. tuberculosis* in a low-incidence setting.

In a cost-effective analysis [201] comparing 6 months and 12 months of isoniazid in the treatment of patients with fibrotic lung lesions in the IUAT trial [68], the cost per case prevented was $7,112 for the 6-month regimen, compared with $16,024 for the 12-month regimen, and each additional case prevented by the 12-month regimen would cost $80,807. Therefore, the 6-month regimen appeared to be more cost-effective, at least under the level of treatment completion and effectiveness as observed in that trial and the costs then prevailing in the United States. The lack of difference between the 6-month and the 12-month arm was based on all patients, and not on patients actually taking the drugs as prescribed. It might be argued that a cost-effectiveness study of a treatment regimen should be based on efficacy under optimised situations, rather than effectiveness before it is being well accepted [76,207]. However, in situations where acceptance and adherence to such preventive treatment are likely to remain suboptimal in absence of major breakthroughs in the current diagnostic and treatment tools, there could be an equally valid challenge to this counter-argument from a pragmatic perspective. Like efficacy, no study has compared the cost-effectiveness of 6 months and 9 months of isoniazid.

Alternative regimens were assessed in other cost-effectiveness analyses. Jasmer *et al.* used a Markov model to conduct a cost-effectiveness analysis based on frequency of adverse events and completion of the 2 treatment regimens in a recent clinical trial. [202] Although 2 months of rifampicin plus pyrazinamide and 9 months of isoniazid both increased life expectancy by 1.2 years as compared to no treatment, the short-course regimen cost 273 dollars more per patient over a range of completion frequencies. In another modelling study focusing on tuberculin skin test converters after recent exposure to an infectious index case, 4 months of rifampicin was cost-saving compared with 9-month therapy of self-administered isoniazid, and directly observed isoniazid plus rifapentine once weekly for 3 months is cost-saving for extremely high-risk patients and cost-effective for lower-risk patients. [198]

In a decision and cost-effectiveness analysis on hypothetical HIV-infected patients with CD4 counts of 200 cells/mm3 or less and positive results on tuberculin skin tests,[205] isoniazid for 6 months or 12 months, isoniazid and rifampicin for 3 months, and rifampicin and pyrazinamide for 2 months were all cost-saving, but a 3-month regimen of isoniazid, rifampicin, and pyrazinamide was not. Short-course preventive therapy appears to be a reasonable alternative to the 12-month isoniazid regimen.

Clinical Perspectives

The purpose of this section is to summarize the clinically relevant aspects of what is known on the subject, so as to facilitate clinical decision by the practicing physicians.

1. How is latent infection with *M. tuberculosis* defined?

Latency, as assayed by the tuberculin skin test and IGRA, is a state of persistent mycobacteria-specific T cell responses in the absence of clinical evidence for tuberculosis disease. Such an operational definition is necessitated by the immunodiagnostic nature of the currently available tools. Whether persisting mycobacteria-specific T cell responses depend on the presence of living mycobacteria is not entirely clear.

2. What is the risk for the development of tuberculosis in an individual with latent infection with *M. tuberculosis*?

Among individuals with positive tuberculin skin test results identified during tuberculosis contact tracing who did not receive preventive chemotherapy, approximately 2-5% will develop active disease in the first two years (Grade B). The

risk of tuberculosis may be substantially higher in individuals identified by a positive IGRA tests result, but conclusive data are still missing (Grade D). The disease risk among test-positive persons is likely to be much lower in absence of recent contact exposure (Grade C). It is also heavily influenced by age and other host factors (Grade C).

3. Why should we treat latent infection with *M. tuberculosis*?

Treatment of latent infection by *M. tuberculosis* offers personal protection for individuals at risk of developing tuberculosis (Grade A). Its contribution towards epidemiologic impact, however, varies with the local epidemiological situation, and depends very much on the success of containing ongoing transmission through the effective diagnosis and treatment of infectious tuberculosis sources (Grade D).

4. Is treatment against latent infection with *M. tuberculosis* cost-effective?

A targeted approach is necessary to maximize the cost-effectiveness in the screening and treatment of latent infection with *M. tuberculosis.* The treatment of latent

infection with *M. tuberculosis* has been found consistently to be cost-effective among target groups with high risk of tuberculosis in industrialized countries (Grade B).

5. Who should be evaluated for the presence of latent infection with *M. tuberculosis*?

Widely accepted target groups for screening include children and young adults who have recently been in close contact with a case of infectious tuberculosis (Grade A), HIV-infected subjects (Grade A) and candidates for TNF-antagonists therapies (Grade A). Controversies exist for other less clearly defined risk groups under different social and epidemiological settings, e.g. immigrants, health care workers, patients with chronic renal failure. A consensus development process through open consultation by a local authoritative body may provide valuable guidance to the individual clinician (Grade D). Sufficient information over benefits and risks should be provided to the targeted subjects to allow an informed choice. In general, screening is indicated only for individuals willing to receive treatment on basis of the screening result.

6. Do the tuberculin skin test and IGRAs differ in the ability to diagnose latent infection with *M. tuberculosis*?

As the IGRAs are not affected by BCG vaccination (Grade B), they may offer an advantage over tuberculin skin test among BCG-vaccinated individuals (Grade C). However, neither test is able to distinguish between recent and remote infection, or reliably predict the subsequent development of tuberculosis. Before a tuberculin skin test or IGRA is administered, the clinician should have a clear idea of what target condition (infection or disease) to screen for and the pre-test odds of that condition in the target group being screened. Application of the likelihood ratios will allow the estimation of the post-test odds (post-test odds = pre-test odds x likelihood ratio) across different clinical and epidemiological settings.[208, 209]

7. Which regimen should be used for the treatment of latent infection with *M. tuberculosis*?

From currently available data, the recommended regimen for treatment of latent infection with *M. tuberculosis* remains isoniazid for 6, preferably 12, and perhaps optimally 9 months among both HIV-infected and non-HIV-infected persons (Grade A). Four months of rifampicin (Grade B) and 3 months of isoniazid plus rifampicin

(Grade A) are acceptable alternatives. Rifampicin alone should be considered if isoniazid is contra-indicated or where drug tolerance is a major concern, while isoniazid plus rifampicin may be preferred among HIV-infected individuals (Grade D).

8. How efficacious is treatment against latent infection with *M. tuberculosis*?

The protective efficacy of 12 months of isoniazid may exceed 90% (Grade B), even though field effectiveness may be substantially lower as a result of non-adherence (Grade A). From limited long-term data on 6 months of isoniazid and other alternative regimens, the protection appears to be short-lasting among HIV-infected persons in areas with high incidence of tuberculosis (Grade B).

9. What is the optimal treatment duration for isoniazid preventive therapy?

Currently, there is no consensus over the optimal treatment duration for isoniazid preventive therapy. Patient acceptance, drug adherence, adverse effects and cost-effectiveness are some of the relevant factors for consideration in formulating local recommendations. If these issues are not of concern, there may be a valid case

for using a longer duration of 9 to 12 months, especially among HIV-infected persons (Grade D).

10. What is the optimal therapy to prevent tuberculosis in contacts of patients with MDR/XDR-tuberculosis with a positive tuberculin skin test or IGRA result?

The optimal therapy for treatment of latent infection with a presumably multidrug-resistant *M. tuberculosis* strain is currently not known. Active surveillance of contacts of multidrug-resistant tuberculosis remains a possible option, especially for those at lower risk of developing clinical disease (Grade D).

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Table 1. Incidence / relative risk of active TB for selected risk factors

	Incidence of Disease among tuberculin-positive subjects (per 1000 person-years)	Relative Disease Risk
Recent TB infection		
Infection <1 yr past	12.9	
Infection 1–7 yr past	1.6	
Old TB scar	2.0–13.6	
HIV infection	35.0–162	
Injection drug use		
HIV seropositive	76.0	
Other	10.0	
Smoking		
Current smokers		2.63
Ex-smokers		1.41
Never Smokers		1.00
Passive smoking		1.49
Body Mass Index		
>=30		0.38
25-<30		0.58
23-<25		0.74
18.5-<23		1.00
<18.5		2.11
Silicosis	68	30
Diabetes mellitus (DM)		
DM vs no DM		1.8–4.1
HBA1c >=7%vs <7%		3.1
Chronic renal failure		10.0–25.3
Gastrectomy		2–5
Jejunoileal bypass		27–63
Renal Transplant		37
Heart Transplant		20-74
Head and neck carcinoma		16

Table 2. Comparison between available tests for LTBI

	Tuberculin Skin Test	QuantiFERON®TB-Gold / IT	T-Spot.TB
Antigens	Purified Protein Derivative	ESAT6, CFP10, TB7.7	ESAT6, CFP10
	(Complex mixture; Potential cross-reactions)	(Specific; Absent in BCG and most NTM)	(Specific, Absent in BCG and most NTM)
Test Method	Skin test: intradermal/multiple puncture;	Whole blood interferon assay;	Blood monocyte spot test;
	Two visits	Single visit	Single visit
Laboratory Support	No; Clinic / bedside procedure	High; Fresh blood delivery;	Highest; Fresh blood delivery;
		No cell separation	Cell separation required
Cost	Relatively Low	High	Highest
Interference by BCG	Yes	No	No
Booster Effect	Yes; problem especially in serial testing	No; result by affected by serial testing	No; result by affected by serial testing
	(two tests > 1 week to exclude booster)	(may be affected by prior TST)	(may affected by prior TST)
Choice of cut-off	5, 10, 15 mm in different clinical scenarios	Single	Single
	Trade-off: sensitivity and specificity	Not fully clarified yet	Not fully clarified yet
	Higher disease risk with larger induration	Not fully clarified yet	Not fully clarified yet
Conversion	Criteria established for recent conversion	Not fully clarified yet	Not fully clarified yet
Infection or Disease	Does not distinguish	Does not distinguish	Does not distinguish
Recent vs Remote	Does not distinguish	Does not distinguish adequately	Does not distinguish adequately
Exposure correlation	Some degree, especially if not BCG-vaccinated	Higher	Higher / Highest
Immune compromise	Affected significantly	Less affected	Least affected
Advance age	Significantly affected	Less affected	Less affected
Proxy sensitivity*	71-82%	QFT-Gold:73-82%;	86-93%

		QFT-Gold IT: 63–78%	
Proxy specificity†	No BCG:95-99%; BCG: low and heterogeneous	No BCG:98-100%; BCG: 94-98%	86-100%
Longitudinal data	Abundant	Scanty	Scanty

***** positive rate among patients with culture-confirmed tuberculosis; † negative rate among low risk individuals

Table 3. Randomized LTBI treatment trials with a placebo / no treatment arm among non-HIV infected persons

Lead Author	Site (Year)	Target population	Regimen*	TB Cases # / Number Treated		RR (95%CI)
				Treatment	Control	
Comstock [62]	Alaska (1962)	Natives (95% Inuits)	H 12m	50/2480	128/2406	0.38(0.27-0.52)
Mount [64]	US (1962)	Household contacts	H 12m	6/1462	12/1348	0.46(0.17,1.22)
Ferebee [63]	US (1962)	Household contacts	H 12m	8/8478	36/8311	0.22(0.10-0.47)
Ferebee [65]	US (1963)	Mental Institution Residents	H 12m	61/12339	173/12499	0.36(0.27-0.48)
Egsmose [69]	Kenya (1965)	Household contacts	H 12–24m	7/325	18/301	0.36(0.15–0.85)
Del Castillo [70]	Philippines (1965)	Household contacts	H 12m	16/126	22/167	0.96(0.53-1.76)
Veening [71]	Netherlands (1968)	Recent TST converters	H 12m	1/133	12/128	0.08(0.01-0.61)
Falk [72]	US (1978)	Men with previous tuberculosis	H 12–24m	7/325	18/301	0.29(0.11-0.79)
Thompson [68]	E. Europe (1982)	Persons with fibrotic lung lesions	H 3m	76/6956	97/6990	0.79(0.57-1.07)
			H 6m	34/6865		0.35(0.24–0.52)
			H 12m	24/6919		0.25(0.16–0.39)
Girling [73]	Hong Kong (1992)	Silicosis patients	H 6m	20/100	34/99	0.58(0.36-0.94)
			HR 3m	19/87		0.64(0.39-1.03)
			R 3m	17/103		0.48(0.29-0.80)
John [74]	India (1994)	Renal transplant/dialysis patients	H 12m	7/92	10/92	0.70(0.28-1.76)

* H: isoniazid; R: Rifampicin; m: month

\# Data for longest period of follow-up within 2 to 5 years used for analysis

Table 4. Adverse Reactions to Drugs Used for Treatment of LTBI

Drug	Reactions		
	Common	**Uncommon**	**Rare**
Isoniazid		Hepatitis Cutaneous hypersensitivity Peripheral neuropathy	Dizziness Seizure Optic neuritis Encephalopathy Haemolytic anaemia Aplastic anaemia Lupoid reactions Arthralgia Gynaecomastia
Rifampicin		Hepatitis Cutaneous hypersensitivity Gastrointestinal reactions Thrombocytopenic purpura Febrile reaction "Flu-like syndrome"	Shortness of breath Shock Haemolytic anaemia Acute renal failure
Pyrazinamide	Nausea Flushing Photosensitization	Hepatitis Vomiting Arthralgia Cutaneous reactions	Sideroblastic anaemia Gout
Ethambutol		Retrobulbar neuritis Arthralgia	Hepatitis Cutaneous reactions Peripheral neuropathy
Ofloxacin / Levofloxacin[a] / Ciprofloxacin / Moxifloxacin[b]	Gastrointestinal reactions Insomnia	Anxiety Dizziness Headache Tremor	Seizure Colitis Haemolysis

[a] Levofloxacin is better tolerated than ofloxacin
[b] Experience on moxifloxacin tolerance is accumulating

Table 5. Randomized LTBI treatment trials with a placebo / no treatment arm among HIV-infected persons

Lead Author	Site (Year)	TST	TB Cases* / Number Treated				RR (95%CI)†		
			H#	HR#	RZ(H)#	Control	H	HR	RZ(H)
Pape [98]	Haiti (1993)	Positive	2/38[a]	-	-	6/25	0.22(0.05-1.00)	-	-
		Negative	2/20[a]	-	-	5/35	0.70(0.15-3.28)	-	-
Whalen[99]	Uganda (1997)	Positive	7/536[b]	9/556	10/462[f]	21/464	0.29(0.12-0.67)	0.36(0.17-0.77)	0.48(0.23, 1.00)
		Anergic	9/395[b]	-	-	10/323	0.74(0.30-1.79)	-	-
Gordin [102]	US (1997)	Negative	4/260[b]	-	-	6/257	0.66(0.19-2.31)	-	-
Hawken [101]	Kenya (1997)	Positive	5/67[b]	-	-	8/69	0.64(0.22-1.87)	-	-
		Negative	11/235[b]	-	-	8/224	1.31(0.54-3.20)	-	-
		Unknown	9/40[b]	-	-	7/49	1.58(0.64–3.85)	-	-
Mwinga [103]	Zambia (1998)	Positive	4/52[c]	-	2/49[g]	11/60	0.42(0.14–1.24)	-	0.22(0.05-0.96)

		Negative	14/178[c]	-	13/173[g]	17/166	0.77(0.39-1.51)	-	0.73(0.37-1.46)
		Unknown	9/122[c]	-	10/129[g]	16/124	0.57(0.26–1.24)	-	0.60(0.28-1.27)
Fitzgerald [105]	Haiti (2001)	Negative	6/126[a]	-	-	4/111	1.32(0.38-4.56)	-	-
Rivero [106]	Spain (2003)	Anergic	3/83[b]	3/82	1/77[h]	4/77	0.70(0.16-3.01)	0.70 (0.16-3.05)	0.25(0.03-2.19)
Mohammed [107]	S. Africa (2007)	Negative	9/48[d]	-	-	6/50	1.56(0.60-5.97)		

*active TB cases within 1 to 3 years of follow-up (variable and with considerable attrition)
H: isoniazid; HR: isoniazid plus rifampicin daily for 3 months; RZ(H): rifampicin plus pyrazinamide or rifampicin plus pyrazinamide plus isoniazid for 2 to 3 months
† regimen vs no treatment / placebo
‡Mostly positive, with 94% >=10mm
[a] isoniazid daily for 12 months ; [b] isoniazid daily for 6 months ; [c] isoniazid twice weekly for 6 months; [d] isoniazid twice weekly for 12 months
[f] Isoniazid plus rifampicin plus pyrazinamide daily for 3 months; [g] rifampicin plus pyrazinamide twice weekly for 3 months; [h] rifampicin plus pyrazinamide daily for 2 months

Table 6. Randomized controlled LTBI treatment trials, comparing efficacy of isoniazid vs other regimens

Lead Author	Site (Year)	TST	Cases* / Number Treated				RR (95%CI)†		
			H#	HR#	RZ(H)#	R#	HR	RZ(H)	R
Whalen [99]	Uganda (1997)	Positive	7/536[b]	9/556	10/462[f]	-	0.81(0.30, 2.15)	0.60(0.23, 1.57)	-
Mwinga [103]	Zambia (1998)	Positive	4/52[c]	-	2/49[g]	-	-	-	-
		Negative	14/178[c]	-	13/173[g]	-	-	-	-
		Unknown	9/122[c]	-	10/129[g]	-	-	-	-
Halsey [112]	Haiti (1998)	Positive	14/370[c]	-	19/380[j]	-	-		-
Martinez [143]	Spain (2000)	Positive	3/21[a]	1/26	-	-	3.71(0.42-33.15)		-
		Negative	1/43[a]	1/43	-	-	1.00(0.06-15.48)		-
Gordin [111]	International (2000)	Positive	29/792[a]	-	28/791[h]	-	-	-	-
Rivero [106]	Spain (2003)	Anergic	3/83[b]	3/82	1/77[h]	-	0.99(0.21-4.75)	0.70 (0.16,3.05)	-

Rivero [113]	Spain (2007)	Positive	4/108[b]	5/103	2/105[h]	-	0.76(0.21-2.76)	1.94(0.36-10.39	-
Non-HIV				-	-	-		-	-
Girling [73]	HK (1992)	Positive§	20/100[b]	19/87		17/103	0.92(0.52-1.60)	-	1.21(0.68-2.1817)

*active TB cases within 1 to 5 years of follow-up (variable and with considerable attrition)
H: isoniazid for 6 to 12 months; HR: isoniazid and rifampicin daily for 3 months; RZ(H):rifampicin plus pyrazinamide or rifampicin plus pyrazinamide plus isoniazid for 2 to 3 months; R: rifampicin daily for 3 months
† isoniazid vs regimen
§Mainly TST-positive
[a] isoniazid daily for 12 months ; [b] isoniazid daily for 6 months ; [c] isoniazid twice weekly for 6 months; [d] isoniazid twice weekly for 12 months; [e] isoniazid daily for 9 months
[f] Isoniazid plus rifampicin plus pyrazinamide daily for 3 months; [g] rifampicin plus pyrazinamide twice weekly for 3 months; [h] rifampicin plus pyrazinamide daily for 2 months; [j] rifampicin plus pyrazinamide twice weekly for 2 months

Table 7. Serious adverse effects in randomized LTBI treatment trials (reported after 1990) with a placebo / no treatment arm

Lead Author	Site (Year)	Cases*/ Number Treated					RR†(95%CI)			
		H#	HR#	RZ(H)#	R#	Placebo	H	HR	RZ(H)	R
HIV-infected										
Pape [98]	Haiti (1993)	0/58[a]				0/60	0.0(0.0- 0.0)			
Whalen [99]	Uganda (1997)	3/536[b]	13/556	26/462[f]		1/464	2.60 (0.27- 24.88)	10.85(1.42- 82.62)	26.11(3.56, 191.6)	
Whalen [99] (anergy)	Uganda (1997)	0/395[b]				0/323	0.0(0.0-0.0)			
Gordin [102]	USA (1997)	24/260[b]				24/257	0.99(0.58-1.69)			
Hawken [101]	Kenya (1997)	11/342[b]				5/342	2.20(0.77- 6.26)			
Mwinga [103]	Zambia (1998)	12/352[c]	-	14/351[g]		3/350	3.98(1.13-13.97)		4.65(1.35-6.05)	
Rivero [106]	Spain (2003)	6/83[b]	15/82	13/77[h]		0/77	12.07(0.69-210.76)	29.13(1.77-478.67)	27.00(1.63-446.3)	
Non-HIV infected										

Girling [73]	HK (1992)	13/173[b]	11/167	7/172	5/167	2.51(0.89-7.04)	2.2(0.76-6.33)	1.36(0.43-4.28)
John [74]	India (1994)	38/92[a]			33/92	1.15(0.72-1.84)		

*Adverse events leading to termination of treatment

H: isoniazid for 6 to 12 months; HR: isoniazid plus rifampicin daily for 3 months; RZ(H): rifampicin plus pyrazinamide or rifampicin plus pyrazinamide plus isoniazid for 2 to 3 months; R: rifampicin daily for 3 months

† isoniazid vs regimen

[a] isoniazid daily for 12 months ; [b] isoniazid daily for 6 months ; [c] isoniazid twice weekly for 6 months; [d] isoniazid twice weekly for 12 months; [e] isoniazid daily for 9 months

[f] Isoniazid plus rifampicin plus pyrazinamide daily for 3 months; [g] rifampicin plus pyrazinamide twice weekly for 3 months; [h] rifampicin plus pyrazinamide daily for 2 months

Table 8: Comparison of serious adverse effects between isoniazid and alternative regimens in randomized trials reported after 1990

Lead Author	Site (Year)	Cases* / Number Treated				RR†(95%CI)		
		H#	HR#	RZ(H)#	R#	HR	RZ(H)	R
HIV-infected								
Whalen [99]	Uganda (1997)	3/536[b]	13/556[p]	26/462[f]		0.24(0.07- 0.84)	0.10(0.03- 0.33)	
Mwinga [103]	Zambia (1998)	12/352[c]	-	14/351[g]			0.85(0.40-1.82)	
Rivero [106]	Spain (2003)	6/83[b]	15/82[p]	13/77[h]		0.40(0.16- 0.97)	0.43(0.17-1.07)	
Halsey [112]	Haiti (1998)	0/370[c]	-	0/380[j]			0.0(0.0-0.0)	
Martinez [143]	Spain (2000)	15/64[a]	5/69[p]	-			3.23(1.25- 8.39)	
Gordin [111]	International (2000)	48/792[a]	-	75/791[h]		-	0.64(0.45-0.91)	
Rivero [113]	Spain (2007)	7/108[b]	7/103[p]	12/105[h]		0.95(0.35, 2.62)!	0.57(0.23-1.38)	
Non-HIV infected								

Girling [73]	HK (1992)	13/173[b]	11/167[p]		7/172[k]	1.14(0.51-2.55)		1.85(0.74-4.63)
Jasmer‡ [121]	US(2002)	8/282[b]		28/307[h]			0.31(0.14-0.68)	
Leung [122]	HK(2003)	2/36[b]		14/40[h]			0.16(0.04-0.70)	
Tortajada [123]	Spain(2005)	8/159[b]		19/133[h]			0.35(0.15-0.80)	
Spyridis [142] (Children)	Greece(2007)	0/232[e]	0/694[q]					0.0(0.0-0.00)
Geijo [210]	Spain (2007)	4/45[b]	2/51[p]					2.27(0.42-12.38)
Menzies [136]	Canada (2004)	8/58[e]			2/58[m]			4.00(0.85-18.64)
Menzies [137]	International (2008)	16/427[e]			7/420[m]			2.25(0.92-5.46)

*Adverse events leading to termination of treatment

H: isoniazid for 6 to 12 months; HR: isoniazid plus rifampicin daily for 3 to 4 months; RZ(H) :rifampicin plus pyrazinamide or rifampicin plus pyrazinamide plus isoniazid for 2 to 3 months; R: rifampicin daily for 3 to 4 months

† isoniazid vs regimen

‡ systematic, rather than randomized, allocation of subjects (by alternate week)

[a] isoniazid daily for 12 months ; [b] isoniazid daily for 6 months ; [c] isoniazid twice weekly for 6 months; [d] isoniazid twice weekly for 12 months; [e] isoniazid daily for 9 months

[f] Isoniazid plus rifampicin plus pyrazinamide daily for 3 months; [g] rifampicin plus pyrazinamide twice weekly for 3 months; [h] rifampicin plus

pyrazinamide daily for 2 months; [j] rifampicin plus pyrazinamide twice weekly for 2 months
[k] rifampicin daily for 3 months; [m] rifampicin daily for 4 months
[p] isoniazid plus rifampicin daily for 3 months; [q] isoniazid plus rifampicin daily for 3 to 4 months

Figure 1: Hypothetical components of the bacterial population in active tuberculosis

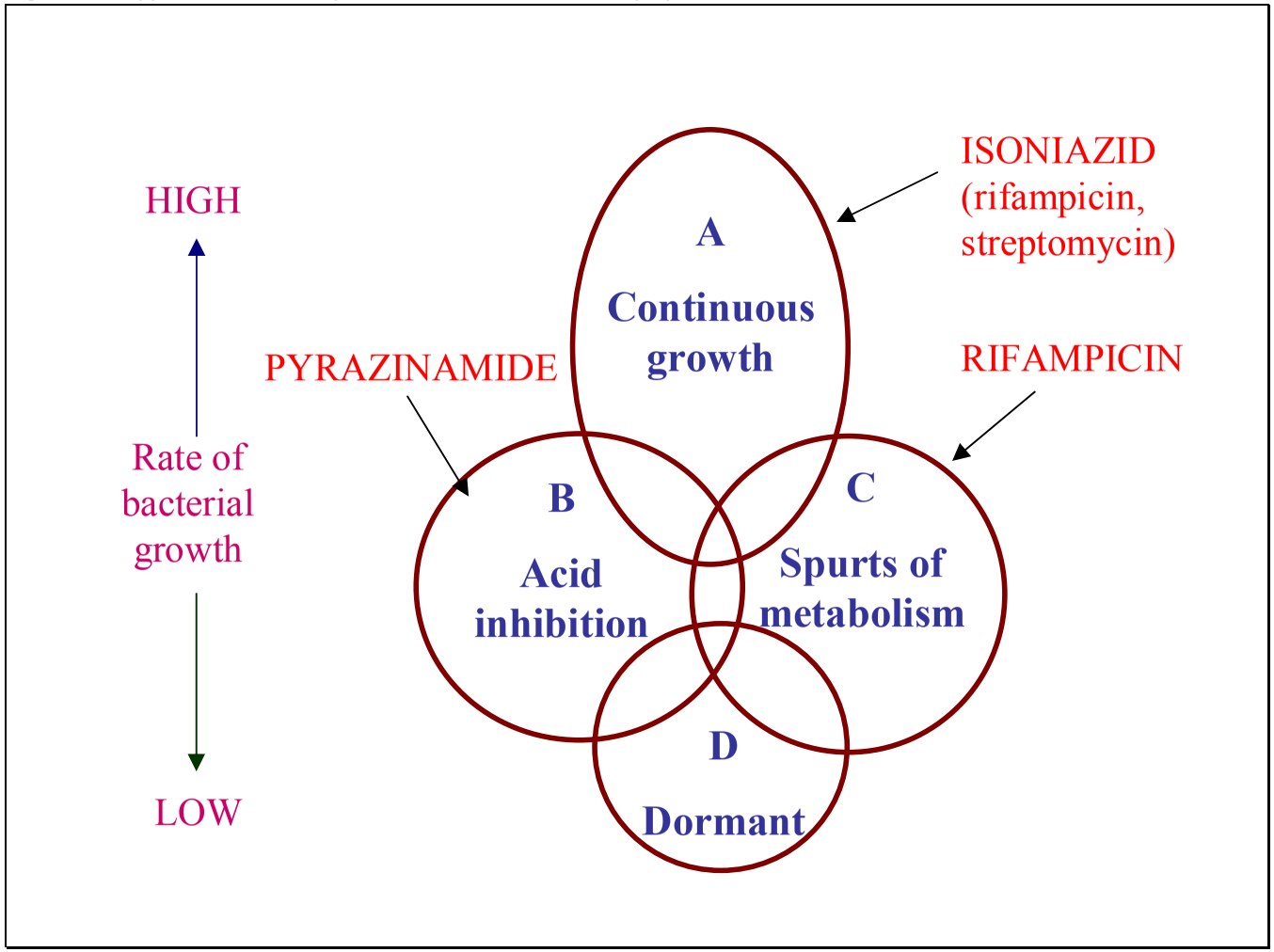
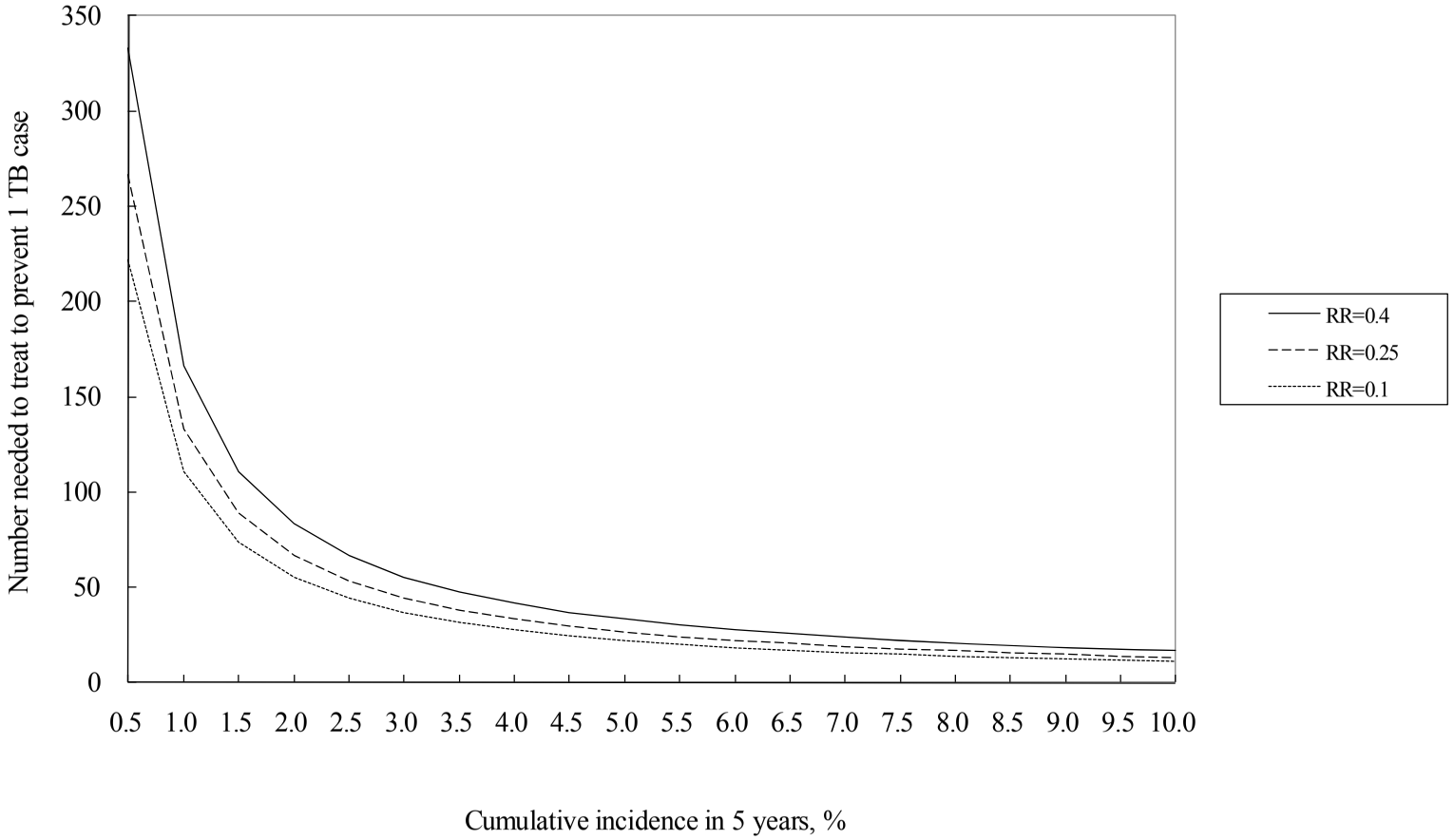
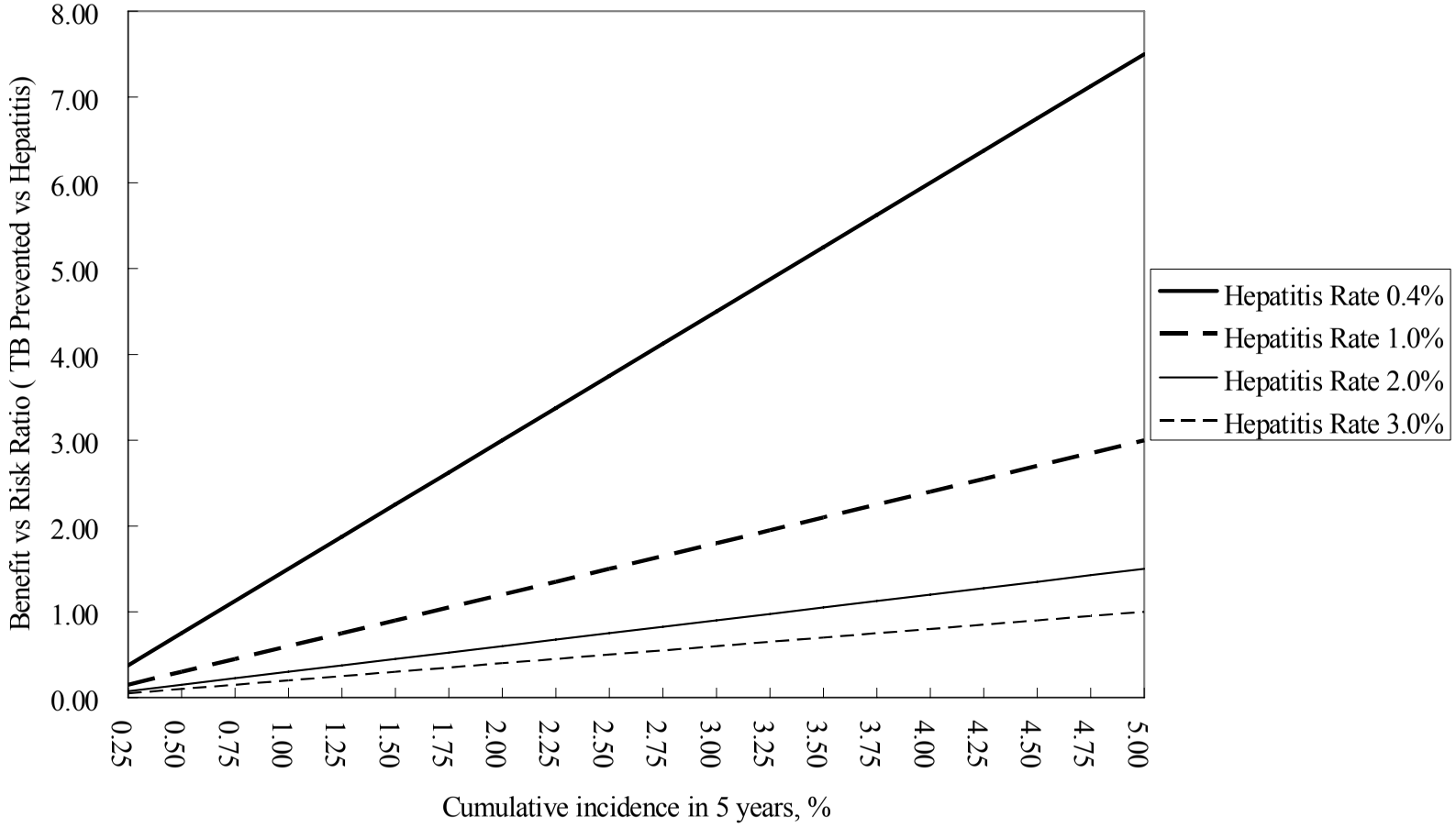


Figure 2: Impact of disease incidence on the number needed to treat to prevent one tuberculosis case within 5 years



RR: risk ratio of treatment vs no treatment

Figure 3: Impact of hepatitis rate and disease incidence on benefit versus risk ratios


Benefit vs Risk Ratio (TB Prevented vs Hepatitis)
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
0.25
0.50
0.75
1.00
1.25
1.50
1.75
2.00
2.25
2.50
2.75
3.00
3.25
3.50
3.75
4.00
4.25
4.50
4.75
5.00
Cumulative incidence in 5 years, %
Hepatitis Rate 0.4%
Hepatitis Rate 1.0%
Hepatitis Rate 2.0%
Hepatitis Rate 3.0%

Appendix: Grading of Evidences for Recommendations (Scottish Intercollegiate Guidelines Network)

Study Rating	Study Design	Number of Studies	Target Population	Grades of Recommendation
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias	At least 1 study	Directly Applicable	**A**
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias	Studies with overall consistency	Directly Applicable	
1++ / 1+	As above		Extrapolated	**B**
2++	High quality case control/cohort studies or their systemic reviews, with very low risk of confounding/bias and high probability of causal relationship	Studies with overall consistency	Directly Applicable	
			Extrapolated	**C**
2+	Well-conducted case control/cohort studies with low risk of confounding/bias and moderate probability of causal relationship	Studies with overall consistency	Directly Applicable	
			Extrapolated	**D**
3	Non-analytic studies, e.g. case reports, case series			
4	Expert opinion			