Treatment of Latent Tuberculosis Infection

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Abstract

Latent tuberculosis infection (LTBI) refers to a circumstance in which viable *Mycobacterium tuberculosis* (*MTB*) bacilli are present in an individual but symptoms and signs of active disease are lacking, and the bacilli are relatively inactive metabolically. In favorable circumstances, some of these inactive bacilli resume greater metabolic activity and replication, leading to the development of active tuberculosis disease. Treatment of this condition (TLTBI) is designed to prevent (soon, or in the distant future) this progression from asymptomatic infection to symptomatic, potentially lethal, active disease. This narrative review draws upon recent reviews of LTBI and seeks particularly to include recently published or presented data that are not included in those prior reviews. Adverse effects of treatment are considered, as are the special circumstances of human immunodeficiency virus–related LTBI, drug resistance, and use of TLTBI in the context of tumor necrosis factor alpha (TNF-α) inhibition. The review describes the main studies underpinning Centers for Disease Control and Prevention recommendations on use of the new 3-month isoniazid-rifapentine regimen and points to evolving data that may support future modification of those recommendations.

Keywords
- latent TB
- TB preventive therapy
- TB prophylaxis
- isoniazid
- 3HP
- rifapentine

Definition and Scope

In latent tuberculosis infection (LTBI) viable *Mycobacterium tuberculosis* (*MTB*) bacilli are present in an individual but symptoms and signs of active disease are lacking, and the bacilli are relatively inactive metabolically. In favorable circumstances, some of these inactive bacilli resume greater metabolic activity and replication, leading to the development of active tuberculosis (TB) disease. Treatment of LTBI (TLTBI) is designed to prevent (soon, or in the distant future) this progression from asymptomatic infection to symptomatic, potentially lethal active disease. Several recent excellent reviews have summarized information on TLTBI (also called TB preventive therapy), and these are recommended to the interested reader.[1–3] This narrative review is part of a new volume summarizing knowledge on diagnosis and treatment of TB. It draws upon those recent systematic and narrative reviews of LTBI but seeks particularly to include recently published or presented data that are not included in those prior reviews. This review describes the main studies underpinning Centers for Disease Control and Prevention (CDC) recommendations on use of the new 3-month isoniazid-rifapentine regimen and points to evolving data that may support future modification of those recommendations.

Concept of Microbial Latency, Dormancy, and Persistence

The terms *latency*, *dormancy*, and *persistence* are not always clearly distinguished. *Latency* refers to the condition of infection without obvious disease (i.e., LTBI). The concept of latency in TB has been present for at least 60 years, since it was demonstrated that future disease in asymptomatic children exposed to infectious adults could be prevented by the timely administration of isoniazid (INH) alone.[4] In the past 25 years, considerable effort has been made to understand better the condition of latency, due in part to the belief that latent surviving bacilli are responsible for relapse after treatment and drive the long-required duration of TB treatment. Effort has been directed to increasing our

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understanding of dormancy, which is a nonreplicating state of reduced metabolic activity, including transcription and translation. Much has been learned about the biological and environmental factors that govern the shifts between the conditions of active metabolism and replication to those of dormancy. It is now recognized that *MTB* is capable of "an extensive repertoire of metabolic realignments to enter a defined nonreplicating state."[5] Wayne and Hayes are credited with first demonstrating an in vitro model of *MTB* dormancy, using gradual depletion of oxygen, and demonstrating a shift in metabolic enzymes, cessation of DNA replication, and reduction but not cessation of RNA synthesis.[6] Since then, multiple other stressful conditions have been shown to favor a shift to latency, including nutritional depletion (amino acids, iron), low pH, exposure to nitric oxide or active oxygen intermediates, and extremes of temperature.[7] The classic studies of McDermott and colleagues established the existence of the state of persistence.[8] Persisting bacilli within a host are viable but nonculturable and are resistant to the action of antibiotics but lacking genotypic resistance; they can be rendered culturable through various interventions, including immunosuppression[9] or the addition of stimulating agents such as the recently described resuscitation promotion factors.[10] It has become clearer that the concept of latency has been oversimplified, and that a useful understanding of the bacillary states variously referred to as latency, dormancy, or persistence will require deeper understanding of microbial physiology and genetics, and the pathological[11] and immunologic[12] responses to infection with *MTB*.[5]

Diagnosis

A separate contribution to this volume discusses diagnosis of LTBI, describing both recent advances and continuing challenges in the diagnosis of a condition for which no true gold standard test exists.

Epidemiology

LTBI remains one of the most prevalent infectious conditions affecting humankind. It is estimated that roughly one third of the global population is infected.[13] In the United States, the National Health and Nutrition Evaluation Survey assessed LTBI prevalence among the civilian, noninstitutionalized, and nonhomeless population in 1999 to 2000 using the tuberculin skin test (TST) and defining LTBI as a positive TST reaction of 10 mm or more. An estimated 11,213,000 (4.2%) individuals had LTBI. Among 25- to 74-year-olds, estimated prevalence had fallen from 14.3% in 1971–72 to 5.7% in 1999–2000. Higher prevalence was noted in the foreign born (18.7%) compared with the US born (1.8%), and among non-Hispanic blacks/African Americans (7.0%), Mexican Americans (9.4%), and individuals living in poverty (6.1%). A total of 63% of LTBI was among the foreign born.[14] Interestingly, the 60% decline in LTBI since 1971–72 among persons aged 25 to 74 was roughly parallel to the 63% decline in reported TB cases since 1972, and the proportion of persons with LTBI who were foreign born represented roughly 60% of the estimated total. A repeat survey was performed in 2011–12 and will be reported soon.

Clinical Relevance

A variety of clinical factors have been recognized as associated with risk of progression from LTBI to active disease (►**Table 1**).[15]

It is remarkable that most tables such as this do not mention the most widely appreciated risk factor for development of TB, namely current or recent treatment of active TB. The notable studies of the British Medical Research Council documented combined failure/relapse rates during or after rifampin-based short-course chemotherapy of 2 to 5%.[16] Patients in these circumstances (during or after the continuation phase of therapy for active disease) are presumed to have only a few dormant (persisting) bacilli. Some of these patients (those with cavitary TB who respond slowly to therapy) have risks of relapse after therapy of 20 to 25%.[17] These rates are clearly higher than those seen in persons identified in contact investigations in the United States, and thus such persons may merit consideration for additional therapy to eliminate LTBI (see Special Circumstances: HIV later in this article)

Animal Models

The most informative animal model of TB has been the murine model. Early murine studies focused on treatment of active disease, but Grosset and Mitchison began in the 1990s to examine models of latent infection as well.[18–20] They used different mouse models that sometimes gave conflicting results..[18,20,21] These studies provided support for the 2-month rifampin and pyrazinamide regimen, as well as for regimens based on weekly rifapentine. More recently, Grosset's group reported on murine studies which suggest that isoniazid (INH) and rifapentine may be effective as TLTBI using very short periods of daily therapy, and bedaquiline may be effective in the treatment of LTBI due to multidrug resistant (MDR) strains.[22,23]

Treatment

The use of anti-TB drugs to prevent development of TB disease among persons known or suspected to be infected with *MTB* began with Edith Lincoln's efforts to prevent progression of primary TB to meningitis among recently exposed children seen at Bellevue Hospital.[4] In 1959 at the Arden House Conference of the U.S. Public Health Service (USPHS) and the National Tuberculosis Association, experts recommended the expanded use of chemotherapy as "preventive therapy."[24] INH preventive therapy was first formally recommended in the United States for persons with previously untreated TB or recent TST conversion in 1965.[25] The recommendation was expanded in 1967 to include persons with specified medical conditions and persons under age 20 with a positive TST.[26] Subsequent modifications in indications and management were made in response to the growing recognition of the

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

Risk factor	Estimated risk for TB relative to
	persons with no known risk factor
High risk (testing and treatment for LTBI recommended for all ages	
AIDS (not on anti-HIV therapy)	110–170
HIV (not on anti-HIV therapy)	50–110
Transplantation (related to immunosuppressive therapy)	20–74
Silicosis	30
Chronic renal failure requiring hemodialysis	10–25
Carcinoma of head and neck	16
Recent TB infection (< 2 years)	15
Abnormal chest X-ray—with upper lobe fibronodular disease typical of healed TB infection	6–19
TNF-α inhibitors	2–9
Moderate risk (testing and treatment for LTBI recommended if age < 65 years)	
Treatment with glucocorticoids	5
Diabetes mellitus (all types)	2–4
Young age when infected (0–4 years)	2–5
Slightly increased risk (testing and treatment for LTBI recommended if age <50 years)	
Underweight (< 90% ideal body weight; for most persons, this is a BMI _ 20)	2–3
Cigarette smoker (1 pack/day)	2–3
Abnormal chest X-ray—granuloma	2
Low risk (testing and treatment for LTBI recommended if age < 35 years)	
Infected person, no known risk factor, normal chest X-ray ("low-risk reactor")	1
Very low risk (treatment of LTBI not usually recommended)	
Person with positive two-step ("boosting"), no other known risk factor, and normal chest X-ray	0.5

Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; LTBI, latent tuberculosis infection; TB, tuberculosis; TNF, tumor necrosis factor.
Source: Modified from Lobue and Menzies[1] and CDC.[15]

hepatotoxicity associated with INH therapy (see later discussion). Inclusion of LTBI treatment in the context of contact investigation elevated preventive therapy in the national strategy to control tuberculosis. The concern about INH toxicity also spurred interest in alternative regimens, and over the past 20 years investigators have assessed several different rifamycin-based regimens, generally of shorter duration, both with and without companion drugs. Increasing recognition of MDR-TB (i.e., TB resistant to both INH and rifampin) and the difficulties encountered in its treatment have stimulated interest in the use of preventive therapy among contacts of MDR-TB.

Efficacy of Drugs and Regimens

Isoniazid Alone

INH was the first anti-TB agent to be employed successfully for preventive therapy, and by far more is known about its performance as a prophylactic therapy than is known for any other anti-TB drug. As soon as INH's remarkable potency was demonstrated, Edith Lincoln, in a classic study, began to use it to prevent progression from primary TB to disseminated forms and meningitis among children at Bellevue Hospital in New York City. Subsequent large trials by the US Public Health Service and others demonstrated the preventive efficacy of INH given for 12 months as daily, self-administered therapy. Trial groups included children with primary TB,[27] Alaskan villagers,[28] residents in psychiatric institutions,[29] household contacts to previously known TB cases[30] or to newly reported active TB cases,[31] and persons with radiographically "inactive" lesions. INH was significantly active in all groups, with 54 to 78% efficacy in adults, and was 100% effective in preventing meningitis and disseminated TB among children with primary TB.[32] A subsequent report on the Bethel, Alaska, studies documented the long-term (at least 19 years) effectiveness of INH.[33] A British Medical Research Council study in rural Kenya administered INH for 12 to 24 months to household contacts of active TB cases and demonstrated 64% efficacy.[34] A study of INH prophylaxis among household contacts in the Philippines assessed

outcome based solely on X-ray changes; efficacy was only 4%, but protection was 42% among those who were TST positive.[35] A study in young Dutch sailors who converted their skin tests after exposure to a single case demonstrated 92% efficacy, attributed to early institution of therapy and high levels of compliance.[36] In a Veterans Administration study of 12 and 24 months of INH among persons with prior active disease, those with no prior chemotherapy had a 60% reduction in culture- or X-ray-defined reactivation; those with prior therapy had no benefit.[37] The largest study of INH prophylaxis ($n = 27{,}830$) was conducted in seven nations of eastern Europe by the International Union Against Tuberculosis (IUAT) and compared three lengths of therapy (3, 6, and 12 months) with placebo for previously untreated TST-positive persons aged 20 to 65 with fibrotic changes on X-ray.[38] This exceptional and careful trial retained over 97% of the persons enrolled. The 5-year rate of TB disease in the placebo arm was 14.3 per 1,000 persons, or 1.43%. Efficacy was 21%, 65%, and 75% in the three INH arms, respectively, and was significantly greater (30%, 69%, and 93%, respectively) among those who completed their assigned durations and collected at least 80% of their assigned medication doses (so-called completer-compliers). An influential cost-effectiveness analysis published in 1986 led to widespread adoption of the 6-month daily INH 300 mg regimen in the United States for treatment of LTBI.[39] Then in 1999 George Comstock published new analyses of data from several studies, including the USPHS household contact study, the Veterans Administration study, the IUAT trial, and the USPHS Bethel, Alaska, studies.[40] His analyses indicated that maximal efficacy occurred with durations of daily INH of 9 to 12 months. This led to a shift in the United States in the recommended duration of INH from 6 to 9 months (9H).[41] Studies in persons with human immunodeficiency virus (HIV) infection are described later in this article.

Rifamycins

The potent sterilizing ability of the rifamycins, coupled with their declining cost and with increasing concerns about INH-associated hepatitis, led to investigations of their utility in preventive therapy. They have been used both alone and in combination with other drugs, notably INH and pyrazinamide. Two outbreaks of INH-resistant TB have stimulated investigation of rifampin-only regimens for prophylaxis among infected contacts.[42,43] These two outbreaks reported on 243 persons treated with rifampin or rifampin plus INH for 6 months; none of these persons developed disease. Assuming an expected rate of disease of 5%, the estimated protective efficacy was at least 70%.

The British Medical Research Council conducted the first randomized trial of rifampin-containing regimens for therapy of LTBI among silicotics in Hong Kong.[44] Sputum culture-negative adult silicotics (over 90% TST positive) were randomized to 3 months of INH and rifampin, 3 months of rifampin only, 6 months of INH, or placebo. Results were as shown in ►**Table 2**.

There was not a statistically significant difference among the three active arms; the placebo arm had significantly more TB cases by 5 years of follow-up. The rifampin-only arm performed more favorably than any other. It also had fewer hepatic reactions reported. INH-resistant TB occurred in all arms, most commonly in the 6H arm; rifampin resistance appeared only in the placebo arm. In the discussion of this trial, the authors commented on the potential utility of long-acting rifamycins such as rifapentine.

In recent years, attention has focused on three types of rifamycin-based short-course regimens for treatment of LTBI. These are (1) 3 to 4 months of rifampin, alone or in combination with INH; (2) 2 to 3 months of rifampin and pyrazinamide; and (3) 3 or fewer months of INH and rifapentine:

(1) Interest in rifampin-only regimens has increased since the option of 4 months of rifampin (4R) was recommended (as an acceptable alternative for INH-resistant LTBI) in the 2000 revision of the US guidelines, largely based on the MRC trial in silicotics (which used only 3 months of R, not 4; ►**Table 2**).[41] On the strength of this recommendation, several programmatic assessments of the 4R regimen have been published.[45–48] Menzies and colleagues in Montreal have been most engaged in the assessment of 4R as an alternative to 9H. They have published a pilot study,[49] a study of adverse events,[50] and two studies of costs[51,52] and are currently guiding a large (planned sample size of 5,720) multinational trial comparing 4R with 9H in the treatment of LTBI.[53] The trial's results will be available in 2016 at the earliest.

Table 2 Results of the British Medical Research Council (MRC) Hong Kong trial of prophylaxis among silicotics[44]

Arm	3R	3HR	6H	Placebo
No. Enrolled	165	161	167	159
% with TST > 9 mm	96%	91%	95%	95%
TB by 5 years[a]	17%	22%	20%	34%
TB by 5 years[b]	10%	16%	14%	27%
Hepatic AE	1 (1%)	6 (4%)	7 (5%)	3 (2%)
No. cases INH-resistant/no. tested	2/15 (13%)	2/21 (10%)	5/19 (26%)	4/28 (14%)

Abbreviations: AE, adverse event; H, isoniazid; HR, isoniazid plus rifampin; INH, isoniazid; R, rifampin; TB, tuberculosis; TST, tuberculin skin test.
[a]Crude % of all patients enrolled.
[b]Life table rate in patients with no interruption.

The use of INH plus rifampin in treatment of LTBI was substantially encouraged by reports of the successful use of this combination in prophylaxis of children in the United Kingdom. Ormerod and colleagues reported three times over a period of 23 years on this combination used for durations of 9, 6, 4, and ultimately only 3 months.[54–56] The use of 3 to 4 months of INH *plus* rifampin has been further studied in two relatively small trials[57,58] reporting on $\leq$ 100 HIV-uninfected persons per treatment arm, and in one larger trial ($N = 926$) of HIV-negative Greek children under age 15 years.[59] Further, several smaller trials,[60–62] and two larger trials,[63,64] involved HIV-infected persons. In general these trials showed no significant differences between the shorter-duration HR combination arms and the longer INH-only arms, which were similarly effective, had similar rates of serious adverse events, and had similar rates of completion of therapy.

(2) The combination of rifampin and pyrazinamide as therapy for LTBI was considered as early as the 1980s.[65] Grosset and colleagues reasoned that since the therapy of active TB had been shortened from 18 to 6 months through the addition to INH of rifampin and pyrazinamide, the addition of either or both drugs might shorten the necessary duration of INH preventive therapy to something well below the 6 months shown to be effective in the IUAT prophylaxis trial.[38] In addition, they pointed out that studies in Hong Kong had demonstrated that smear-negative and culture-negative TB disease could be effectively treated with 4, 3, or even 2 months of a four-drug regimen (►**Table 3**).[66] If culture-positive relapse were considered in the 1976 study to represent progression of LTBI, then the daily four-drug 3-month regimen was 88% effective after 5 years of follow-up.

Grosset's studies tested the efficacy of rifampin alone or in combination with INH and/or pyrazinamide in a murine model of LTBI.[65] Surprisingly the most effective regimens were 2 months of rifampin-pyrazinamide or 3 months of rifampin alone. This work created great interest in the potential of a 2-month LTBI regimen of rifampin-pyrazinamide (2RZ). Further, most experts consulted by the World Health Organization (WHO) were at the time unwilling to recommend a regimen using rifampin alone, for fear of engendering rifamycin resistance (pers. comm., Dr. R. O'Brien). Several substantial trials of 2- to 3-month RZ regimens were then undertaken: one in Haiti,[67] one in Zambia,[68,69] and one as a multinational trial (in the United States, Brazil, Haiti, and Mexico).[70] These trials all sought to enroll only persons who were HIV-infected and not on antiretroviral therapy (ART) because such persons have a rapid rate of progression from TB infection to disease, and the resultant higher event rates and smaller sample sizes would permit more rapid completion of the trials. All three trials found that 2 to 3RZ was as effective as 6 months of INH. Several small, unpublished pilot studies reported adequate tolerability in HIV-negative persons; as a result, the regimen was recommended for use in the United States.[41] Shortly following publication of these recommendations, reports of severe hepatotoxicity began to appear.[71–73] Overall 50 cases and 12 deaths in the United States were attributed to the regimen,[74] which was shown to have rates of severe hepatotoxicity and death significantly in excess of those associated with INH.[75] By 2003 the 2RZ regimen was no longer recommended, except in very limited circumstances.[76]

(3) Two decades after the authors of the Hong Kong study of silicotics had speculated about an LTBI treatment regimen using rifapentine, three different trials reported on the performance of a regimen of once-weekly INH and rifapentine (►**Table 4**).[77–79] Murine models had supported the use of such a regimen.[80–83] The three human trials were performed in Rio de Janeiro, in Johannesburg, and in the United States, Canada, Brazil, and Spain. The first trial randomized participants either to 2 months daily rifampin and pyrazinamide or to 3 months once-weekly INH 900 mg plus rifapentine 900 mg.[77] This trial was halted early due to an elevated rate of hepatotoxicity in the 2RZ arm. Most of the participants were TST-positive, HIV-negative household contacts to active cases. Adherence was high, and both regimens appeared effective; the 2RZ regimen had fewer cases (one vs three) but the rates were low and not significantly different (0.5% vs 1.5%). Studies in Boston and in Rio de Janeiro had indicated that 8 to 9% of infected close or household contacts develop active disease if untreated.[42,84] The second study randomized

Table 3 Therapy of smear-negative and culture-negative TB disease in Hong Kong[66]

Study	Smear	Culture	Regimen	Duration (months)	Assessed	Relapse at 24 months (%)	Relapse at 60 months (%)
1 (1976)							
1	Negative	Positive	SHRZ	2	72	22	32
1	Negative	Positive	SHRZ	3	69	12	13
1	Negative	Negative	None	—	176	53	57
1	Negative	Negative	SHRZ	2	165	7	11
1	Negative	Negative	SHRZ	3	162	4	7
2 (1978)							
2	Negative	Negative	SHRZ	3	364	2	6
2	Negative	Positive	SHRZ	4	157	3	3

Abbreviations: SHRZ, streptomycin, isoniazid, rifampin, pyrazinamide; TB, tuberculosis.

Table 4 Trials of once-weekly isoniazid 900 mg + rifapentine 900 mg in LTBI

Study (enrolling period)	Population	Arm	Frequency	Enrolled	DOT doses	TB (n)	(S)AE	Death (n)	Completion	LTFU
Schechter 2006[77]	TST positive HH contacts, 99.5% HIV negative	2RZ	Daily	193	1 of 7	0.52%	10%	3%	94%	2%
		3HP	Once-wkly	206	All	1.46%	1%	1%	93%	2%
2001–2005							(Gr 3–4 hepatotox)			
Martinson 2011[78]	TST positive, HIV positive adults	3HP	Once-wkly	328	All	7% (24)	66%	11% (17)	96%	23% not seen in last 6 mos or known dead
		3HR	Twice-wkly	329	All	7% (24)	64%	11% (16)	95%	
2002–2005		Cont H	Daily	164	None	5% (8)	84%	9% (8)	89%	
		6H	Daily	327	None	7% (22)	66%	13% (25)	84%	
Sterling 2011[79]	TST positive close contact or converter 95%; HIV+ 3%	3HP	Once-wkly	3,986	All	0.18% (7)	1.6%	0.8%	82%	12%
2001–2008		9H	Daily	3,745	None	0.40% (15)	2.9%	1.0%	69%	14%

Abbreviations: DOT, directly observed therapy; H, isoniazid; HH, household; HIV, human immunodeficiency virus; HP, isoniazid/rifapentine; HR, isoniazid plus rifampin; LTBI, latent tuberculosis infection; LTFU, lost to follow-up; RZ, rifampin + PZA; S(AE), serious adverse event; TST, tuberculin skin test.

HIV-infected TST-positive adults with CD4 cell counts > 200 to one of four regimens: 3 months of directly observed, once-weekly INH and rifapentine (3HP; $n = 328$); 3 months of twice-weekly INH and rifampin also by directly observed therapy (DOT) ($n = 329$); 6 months of self-administered daily INH ($n = 327$); or continuous self-administered INH ($n = 164$).[78] Adherence was high for all four regimens. There were no significant differences among the four regimens in rates of active TB (range 1.4 to 2.0 per 100 person-years) or death (range 1.3 to 2.1 per 100 person-years). The continuous INH regimen was nonsignificantly more favorable with regard to these two outcomes but sustained significantly more adverse events during the longer course of therapy. Also of concern was the occurrence of one rifampin-monoresistant TB case among persons given the 3HP regimen, suggesting the possibility that incipient TB disease remains difficult to exclude with certainty during screening of patients in this high-risk setting.[85] The third trial, TBTC (TB Trials Consortium) Study 26, was the largest comparative US trial of preventive therapy in the past 40 years, enrolling 8,053 participants.[79] It randomized subjects to either 9 months of daily self-administered INH 300 mg (9H) or 3 months of once-weekly INH 900 mg and rifapentine 900 mg (3HP). Included were TST-positive close contacts to active TB (~ 70% of persons enrolled), documented recent TST converters (~ 26%), HIV-positive persons with positive TST or recent TB contact (2%), or TST-positive persons with fibrosis on chest X-ray (2%). Completion of therapy was 69% in the 9H arm and 82% in the 3HP arm. Twenty-two cases occurred during the 33 months of therapy and observation; the rates were 0.43% in the 9H arm and 0.19% in the 3HP arm, sufficient to satisfy the criteria of noninferiority specified in the trial's revised analytic plan. The event rates were low in this trial; among 384 subjects who received two doses or less of combination therapy, or less than 30 days of INH only, but who remained in the study, there were four tuberculosis cases, for a cumulative rate of 1.64%. This was, however, comparable to the rates observed in the IUAT (5-year incidence in the placebo arm of 1.43%)[38] and USPHS-Contact studies.[32]

Of the 22 cases, 20 were confirmed on culture. There were two INH-resistant cases (both in the INH-only group) and one rifampin-resistant case (in the 3HP arm). The latter case occurred in a subject with HIV infection (CD4+ cell count = 271 per mm^3 at enrollment) and INH-susceptible *M. bovis* infection (also considered to be culture-confirmed TB) who had treatment interruptions and completed therapy late. This was one of the very few recent studies that enrolled children. Because the numbers of persons with HIV and the numbers of children were low, enrollment of these two groups was extended; ultimately 393 HIV-positive persons and 539 children under 12 years of age were enrolled. Many of these HIV-positive persons are still in follow-up, with final results expected in 2013. Preliminary assessment indicated that, among HIV-positive persons not receiving ART, 3HP was better tolerated and had higher treatment completion rates than 9H for treatment of latent *M. tuberculosis* infection.[86] Similar findings concerning tolerability of 3HP applied to children aged 2 to 17 years; moreover, efficacy data in

children were presented when 96% of follow-up had been completed, and noninferiority of 3HP was affirmed in this important age group.[87]

Serious adverse events occurred in 1.6% of 3HP patients and 2.9% of 9H patients. Investigator-assessed drug-related hepatotoxicity occurred in 0.4% and 2.7%, respectively. Possible drug-related hypersensitivity occurred in 3.8% and 0.5%. The adverse event experience in this open-label trial was complex, and detailed analysis is still under way. Six of the suspected hypersensitivity occurrences involved hypotensive episodes (systolic BP < 90). Some of these adverse event episodes likely represent rifamycin hypersensitivity, or "flu-like syndrome."[88,89] Hypersensitivity and flulike syndrome have been reported with other long-acting rifamycins.[90,91] The experiences with hepatotoxicity due to INH and to 2RZ noted earlier have led to increased caution surrounding the introduction of new LTBI regimens; concern also persists regarding the potential for once-weekly rifapentine regimens to foster the development of rifamycin resistance in persons with active TB and advanced HIV.[86]

Nevertheless, compared with 9 months of INH, the potential logistical advantage of an effective and well-tolerated 3-month regimen for LTBI is enormous. Simultaneous with publication of the Study 26 findings, CDC published guidelines for use of the new 3HP regimen in the United States.[92] Those guidelines recommended use of the 3HP regimen as an equal alternative to the 9-month INH regimen for many persons $\geq$ 12 years of age; future publication of the pediatric data cited earlier may lead to modification of the recommended lower age limit. Due to lack of data, the 3HP regimen was not recommended for use in persons with HIV on ART; if permissive data on interaction with ART become available, then use of the 3HP regimen in HIV-infected persons receiving ART might be reconsidered. CDC's TB Trials Consortium began in 2012 a trial assessing self-administration of this 12-dose regimen; if findings from this trial support self-administration, then the current recommendation that the regimen be given under direct observation may be modified. CDC's TB Epidemiologic Studies Consortium has begun a large (expected enrollment $>$ 40,000) observational study of LTBI at 20 US sites. CDC has initiated an additional multisite phase 4 implementation trial of 3HP. Finally, the existing CDC system for surveillance of severe adverse reactions to any LTBI regimen[93] includes a focus on the new 3HP regimen.

Interest in even shorter HP regimen is strong. Based on promising data from murine studies,[22,23] the Adult AIDS Clinical Trials Group network has begun a study of an ultrashort daily regimen of INH 300 mg and rifapentine (300 to 600 mg, based on weight) given for 4 weeks to HIV-infected persons with positive TST or living in a high-burden country.[94] If successful, it is likely that such a regimen would be studied in HIV-negative persons as well.

Adverse Effects

Isoniazid

Adverse effects from anti-TB medications have been described throughout the history of TB pharmacotherapy, but there are perplexing events scattered throughout this history. The greatest amount of data relate to the hepatic toxicity of INH. Toxic effects of INH were relatively modest in the original studies in children and did not pose a major problem in the large USPHS studies reported by Ferebee.[32] Ferebee reported three cases of jaundice in the USPHS trial in persons with inactive lesions, and one in a trial involving silicotics. A subsequent programmatic study found three cases in $\sim$ 300 participants. Because this study used the same source of INH as the earlier USPHS trial, suspicion was aroused that some contaminant was present and responsible. Several years later, in February 1970, after a report of seven cases of TB among employees working on Capitol Hill in Washington, DC, 2,321 government workers began preventive therapy with INH. Over the next 9 months, 19 persons developed clinical signs of liver disease, including 13 with jaundice; 2 persons died. In a comparison group of 2,154 workers not taking INH, only one had hepatitis.[95] In response, greater screening and monitoring of candidates for INH prophylaxis were recommended.[96] CDC convened an ad hoc committee of experts, which recommended that surveillance for INH-associated hepatitis be undertaken.[97] A surveillance study was conducted in 1971–72 involving 13,838 persons on INH preventive therapy in 26 US health departments.[98] Suspected hepatitis cases were reviewed by a panel of three experts and designated as probable or possible cases, in part on the basis of observed SGOT (serum glutamic oxalo-acetic transaminase) levels. There were 92 probable and 82 possible cases, representing rates of 6.6 and 5.5 per 1,000 persons. Adjusting for age and time in study revised these estimates to $\sim$ 10 per 1,000 each. Among probable cases there were strong associations with age, Asian race, and daily alcohol consumption. There were seven deaths in the probable group and one death in the possible group. These findings led to a further revision of US guidelines for INH prophylaxis, with exclusion of persons aged over 35 years.[99]

Not surprisingly, these reports generated continuing concerns about the frequency of INH-associated hepatotoxicity. In the IUAT study, hepatitis attributable to INH therapy occurred in $\sim$ 2% of persons in the first 12 weeks, and $\sim$ 1% more in each subsequent 3-month period (cumulative rate $\sim$ 5%).[38] A series of cost-benefit studies has assessed the relative value of INH preventive therapy in the face of these potential risks.[100–104] In 1983 the prophylaxis guidelines were again revised to recommend clinical and biochemical monitoring for persons over the age of 35 years.[105] Use was diminished, but considerable prophylaxis continued, especially among TB programs. An analysis using outcome data from the IUAT prophylaxis study concluded that 24 weeks was the most cost-effective duration for INH preventive therapy.[106] INH-associated hepatitis has remained a troubling complication of TB preventive therapy. Two assessments of mortality rates from INH hepatitis in the 1990s reported similar rates (1 to 2 and 4 per 100,000), but came to divergent conclusions on the significance of this continuing challenge.[107,108] One characterized the rate as negligible, whereas the other concluded that "careful patient selection, education, and monitoring are critical." Similar rates of liver failure ($\sim$ 3 per 100,000) have been reported among

children.[109] Nolan et al in Seattle-King County reported a very low rate (0.1%) of hepatotoxicity (and zero deaths) among 11,141 persons starting INH preventive therapy in a carefully monitored clinic program between 1981 and 1995.[110] Variations in case definitions may account for some of this reported variation.[111] Influenced by the more benign recent reports, the 2000 US guidelines on TB prophylaxis recommended routine biochemical monitoring only in persons with preexisting liver abnormalities, symptoms of liver disease, or risks for hepatic disease.[41] An updated guideline on TB prophylaxis is currently being developed. CDC has continued to receive reports of severe INH hepatotoxicity, summarized in 1993[112] and again in 2010.[93] More recently the McGill group has produced informative evaluations of the toxicity of anti-TB therapy, used both for treatment of disease and for LTBI.[113,114] These well-designed studies have again strongly implicated INH as a cause of serious hepatotoxicity, especially among persons aged over 65 years.

Other adverse effects from INH include rash and hypersensitivity, neurological toxicities including peripheral neuropathy (preventable with supplemental pyridoxine) and seizures, rare hematologic effects, unusual lupus-like syndromes, drug interactions due to inhibition of multiple cytochrome P450 enzymes,[115] toxicity from drug overdoses, and reactions due to monoamine poisoning.

Rifamycins

Rifamycins have proven to be relatively safe drugs, with over 40 years' experience in their use. The best known of their side effects is the induction of cytochrome P450 enzymes, particularly CYP3A4, with a resultant increase in the metabolism of a wide variety of drugs (including anticoagulants, oral contraceptives, methadone, and anti-HIV protease inhibitors).[116] Other recognized toxicities include hepatotoxicity (significantly less than with INH), and a variety of severe reactions thought to be immunologic in origin. These include hematologic reactions such as thrombocytopenia and hemolytic anemia, renal reactions such as acute tubular necrosis and interstitial nephritis, and flulike syndrome.[89] These immunologic reactions are believed to occur more often when therapy is intermittent and possibly with higher doses,[88,117] and may be due to antibody-mediated reactions.[118,119]

Cost Considerations

Much of the attractiveness of preventive interventions lies in their potential to reduce costs. Cost-effectiveness analyses have had an important impact upon the uptake of LTBI therapy. The early appeal of such measures derived from the expectation that TLTBI would avert deaths in both children and adults. Enthusiasm was tempered by the early experiences with INH-related hepatotoxicity. Although the IUAT study found greatest protection with 12 months of INH, a subsequent cost-effectiveness study using rates from this trial found that 6 months of therapy provided the optimal cost benefit, compared with 3 or 12 months.[39] A substantial number of cost-effectiveness studies have assessed the utility of TLTBI in persons with HIV,[120] in persons injecting drugs[121] or on methadone maintenance,[122] in schoolchildren,[123] in persons over the age of 35,[103,104] in contacts to TB cases,[124] and in persons receiving INH,[125] rifampin,[126–128] and rifapentine[129,130] in differing rhythms. Interestingly virtually all have found TLTBI to be a cost-effective intervention.[131] Most were performed in high-income settings, and there are fewer studies suggesting that TLTBI is cost-effective in medium or low-income settings. Many, however, rely on assumptions that are uncertain at best; in particular many assume the cumulative rate of TB disease after infection to be 5 to 10%, a figure widely published but poorly documented. Recent assessments of both old and new studies suggest that the rate of *preventable* TB disease may be appreciably lower, in the range of 2%. Such lower rates of eventual disease may lower the cost utility of TLTBI, and further studies are needed.

Special Circumstances

HIV

TB appeared early as a risk among persons with immunodeficiency due to HIV infection.[132] The effectiveness of treating LTBI among persons with HIV was soon demonstrated in Haiti and the United States.[133,134] Multiple subsequent trials helped to establish the effectiveness of this intervention; the Cochrane review by Akolo et al included 12 trials with a total of 8,578 randomized participants.[135] Akolo et al found that TB preventive therapy with any anti-TB drug versus placebo was associated with a statistically significant 32% lower incidence of active TB (RR 0.68, 95% CI 0.54 to 0.85). Efficacy was similar for all regimens (regardless of drug type, frequency, or duration of treatment). However, compared with INH monotherapy, short-course multidrug regimens were much more likely to require discontinuation of treatment due to adverse effects. Although there was reduction in mortality with INH monotherapy versus placebo among individuals with a positive TST (RR 0.74, 95% CI 0.55 to 1.00), and with INH plus rifampicin versus placebo regardless of TST status (RR 0.69, 95% CI 0.50 to 0.95), overall, there was no evidence that TB preventive therapy reduced all-cause mortality compared with placebo (RR 0.94, 95% CI 0.85 to 1.05). There is a substantial literature now indicating that little if any reduction in TB incidence is obtained by treating persons with negative TST and no history of TB contact.[136–141] The review by Akolo et al reported that individuals with a positive TST had a significant 62% reduction in incident TB, whereas those with a negative TST did not have a significant benefit (RR 0.89, 95% CI 0.64 to 1.24).[135] This is consistent with a review of 11 studies (both HIV negative and HIV positive) by Watkins et al, who reported a positive association between TST reactivity and incidence of TB.[142]

Interestingly, this effect of TST-positivity was also quite strong in the recently reported Botswana randomized trial by Samandari et al comparing 6 and 36 months ("continuous") of INH in HIV-positive persons.[143] The authors reported a 43% reduction in TB incidence (2.0% vs 3.4%) among those receiving 36 months of INH compared with 6 months. TB incidence in those individuals receiving placebo escalated $\sim$ 200 days after completion of open-label INH. Participants whose TST

showed $\geq$ 5 mm induration at enrollment received a substantial benefit from continuous INH treatment (hazard ratio [HR] 0.26; 95% CI 0.09 to 0.80, $p = 0.02$), whereas the effect in participants who were TST-negative was low and not significant (HR 0.75, 95% CI 0.38 to 1.46, $p = 0.40$). Such findings are consistent with the presumption that incident TB was due largely to reactivation of LTBI rather than reinfection due to reexposure to active TB in this high-burden setting.

Findings such as this have fueled discussion about the WHO's strategy of providing INH-based preventive therapy (IPT) to all persons with HIV in high-burden TB settings; greater efficiency might be achieved by the wider application of cost-effective diagnostics for LTBI, such as the TST. Current WHO recommendations recognize this challenge, while recommending use of IPT in all persons with HIV if the TST is positive or unknown (i.e., in settings where TST testing is not feasible).[144]

Attention has also been directed toward the impact of ART upon TB incidence in settings of high HIV and TB prevalence. The effect of IPT in the Botswana study was independent of and additive to the TB-preventive effect of ART. By study completion, 946 (47%) of 1995 participants had initiated ART. Regardless of TST status, TB incidence was reduced by $\sim$ 50% in those receiving 360 days of ART compared with participants receiving no ART (adjusted HR 0.50, 95% CI 0.26 to 0.97). In those on continuous INH who also received ART, the reduction was 96% (HR 0.04, 95% CI 0.005 to 0.35). A recent systematic review reports an overall hazard ratio of only 0.35 in persons with HIV and on ART while living in developing countries.[145] Another such review found that, even throughout ART and despite achievement of high CD4 cell counts, TB incidence remains over fourfold greater than in persons without HIV.[146] A recent trial of IPT given for 12 months to persons with HIV who were on or beginning ART in Cape Town, South Africa, reported a 37% reduction in hazard of TB; most of the reduction appeared to occur during the active INH treatment period and diminished during later follow-up, and there was no significant mortality benefit.[147]

Further, TB preventive therapy does not appear to prevent death among persons with HIV who are TST-negative,[137–139,141,142] in contrast to earlier speculation that many such persons might be TB-infected but anergic due to advanced HIV disease.

Another area of debate is that of secondary prophylaxis in persons already treated for active TB. At least two trials have demonstrated benefit from such an approach.[148,149] These two trials both demonstrated substantial benefit when HIV-infected persons completing treatment for active TB were given an additional 6 months of INH or INH plus rifampin therapy (however, both studies employed a relatively weaker twice-weekly continuation phase, and a regimen of only 6 months overall).

The CREATE Studies

Interest in strategies to prevent TB among persons with HIV in high-prevalence settings led the Bill and Melinda Gates Foundation to fund CREATE (Consortium to Respond Effectively to the AIDS/TB Epidemic).[150] CREATE included three large-scale, cluster-randomized studies of strategies to diminish death and disease from TB in communities with high rates of HIV/AIDS; each included some element of LTBI treatment with INH:

1. In the Thibela TB study in South Africa, all 80,000 employees in 15 randomized mine shafts received either standard care or enhanced TB mobilization and screening and access to 9-month IPT. This was the largest trial of IPT ever undertaken. The incidence rate ratio (IRR), adjusted for gender, age, and place of work, was 1.0 (95% CI 0.77 to 1.31); prevalence was also unaffected (PRR 0.95, 95% CI 0.83 to 1.10). Failure to obtain a population effect was attributed to a high rate of nonadherence to IPT. At the individual level, among persons who started IPT, the IRR in months 0 to 8 was significantly lower (aIRR [adjusted incidence rate ratio] = 0.37, 95% CI 0.19 to 0.72), corresponding to a 63% decrease in TB incidence compared with controls. However, this effect was not durable, with IRRs of 1.0 and 0.79 in the periods 9 to 18 months and $>$ 18 months following the IPT treatment period.[151]
2. In the ZAMSTAR study, in Zambia and South Africa, 24 communities (total population $\sim$ 962,000) were randomized to each of two separate interventions: (a) enhanced case finding at clinic, school, and community levels; and (b) a household intervention using the TB patient as the gateway into the household, to offer group education, home-based screening for TB and HIV, and increased access to IPT and ART through counseling and referral. The ZAMSTAR outcomes were survey-measured prevalence of TB and rate of TB transmission measured as change in TST-positivity among school-aged children (►**Table 5**).[152]
3. The third CREATE study, called THRio, was a phased implementation study (using a stepped-wedge design) of tuberculin skin testing and INH preventive therapy (IPT) for TST-positive ($\geq$ 5 mm) persons in 29 HIV clinics in Rio de Janeiro, Brazil.[153] The primary end points were

Table 5 ZAMSTAR risk and rate ratios at the community level, comparing communities with intervention to those without

Outcome	Enhanced case finding	Household intervention
TB Prevalence outcome (risk ratio)	927 vs 711 per 100,000 aRR 1.11 (95% CI 0.87–1.42)	746 vs 883 per 100,000 aRR 0.78 (95% CI 0.61–1.00)
TB Transmission outcome (rate ratio)	0.87 vs 1.71 per 100 py aRR 0.45 (95% CI 0.20–1.05)	1.41 vs 1.05 per 100 py aRR 1.36 (95% CI 0.59–3.14)

Abbreviations: aRR, adjusted risk (or rate) ratio; CI, confidence interval; py, person-years; TB, tuberculosis.

Table 6 Hazard ratios for primary outcomes in ITT and mITT populations in the THRIO study

Outcome	ITT (HR (95% CI); *p*-value)	mITT (HR (95%CI); *p*-value)
Tuberculosis	Adj. 0.73 (0.54–0.99) $p = 0.04$[a] Unadj 0.87 (0.68–1.10); $p = 0.23$	Adj. 0.42 (0.29–0.60) $p < 0.001$[a] Unadj 0.57 (0.44–0.76); $p< 0.001$
Tuberculosis or death	Adj. 0.68 (0.57–0.83) $p < 0.001$[a] Unadj 0.72 (0.62–0.82); $p = 0.001$	Adj. 0.44 (0.35–0.55) $p < 0.001$[a] Unadj 0.56 (0.47–0.66); $p < 0.001$

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mITT, modified intent-to-treat.
Note: The THRio intervention reduced TB 27% by ITT and 58% in mITT analysis, and TB/death 32% and 56%, respectively.
[a]Adjusted for sex, age, time-varying CD4 and highly active antiretroviral therapy (HAART), and excluding patients with unknown CD4.

incidence of TB and TB or death at the clinic level before and after the intervention. Intent-to-treat (ITT) analysis included all eligible individuals enrolled; modified ITT (mITT) analysis considered participants who remained in clinic contact at least annually ("stayers"). Crude rates of TB and TB/death in the control period were 1.31 and 3.67/100 person-years (PYs) versus 1.10 and 3.01/100 PYs in the intervention period. Adjusted and unadjusted ITT and mITT Cox regression results are shown in ►**Table 6**.

Taken together, findings from the three CREATE trials suggest that IPT can have a substantial impact on TB in communities with high rates of HIV, but that impact can be vitiated by lack of adherence and is likely enhanced by targeting of IPT to those with positive TST reactions. Analysis of these remarkable trials is still in an early stage, and discussion of their results and implications is likely to continue for some years.

Drug Resistance

Two issues have arisen with regard to drug resistance and TLTBI:

1. The first concerns the potential to create resistance through the use of single-drug therapy. Ferebee concludes in a 1970 review that INH resistance does not occur more frequently in cases developing after INH prophylaxis than in cases developing after receipt of placebo, but the evidence cited is highly incomplete.[32] Balcells et al reported that treatment of LTBI with INH was associated with a nonsignificant 1.45-fold higher risk of INH-resistant TB compared with the background incidence in the same population.[154] They assessed trials among HIV-negative and HIV-positive populations separately. It is safe to say that there are only limited reports of INH resistance in cases occurring after prophylaxis, consistent with the current view that LTBI is a paucibacillary state in which the bacillary populations are low enough to make spontaneous resistance mutations unlikely. However, it is also clear that failure to eliminate subclinical disease, which is not uncommon in HIV-positive populations in high-burden settings, could expose persons receiving INH prophylaxis to a significant risk of acquired resistance to INH. The same problem might exist with rifamycin-based LTBI treatment regimens. Acquired resistance to rifampin has not been reported as a frequent problem with rifampin-based regimens, but the existing database is relatively modest. Of the three trials that have assessed once-weekly rifapentine-based regimens, two have reported acquired rifamycin resistance. TBTC Study 26 noted that one of seven cases in the once-weekly arm (occurring among 3,986 persons in that arm, of whom 105 were HIV-infected) occurred in an HIV-positive patient with rifampin-resistant *M. bovis*.[79] Resistance was not reported among the three cases (out of 206 persons) that were diagnosed in those receiving once-weekly therapy in the Brazil trial; only 1 of the 206 was HIV-positive.[77] In the Soweto trial in HIV-infected persons, one case of MDR-TB was noted in the once-weekly INH-rifapentine arm, and one in the continuous INH arm; in addition, one case of rifampin monoresistant TB was diagnosed among 21 culture-confirmed TB cases in the rifapentine arm ($n = 328$).[78] Thus, in three prophylaxis trials there have been two rifampin-monoresistant TB cases among 434 HIV-infected persons receiving prophylaxis. None of these trials admitted persons on ART; it would be helpful if acceptable ART could be defined for the once-weekly regimen.
2. The second involves the use of preventive treatment for persons exposed to drug-resistant TB. In the case of INH resistance, the use of rifampin-based preventive therapy has been noted earlier. For prophylaxis of MDR-LTBI (LTBI due to multiple-drug-resistant TB), a variety of regimens have been tried (notably regimens of a newer fluoroquinolone, with or without a companion drug such as ethambutol, pyrazinamide, or ethionamide, or combinations of two of the latter drugs). Only relatively small case series are available to assess such regimens.[155] A recent Cochrane review found no trials of MDR prophylaxis suitable for a systematic review.[155] The same authors reviewed two case series and concluded that INH was not effective and that individualized therapy could be useful.[156] There is considerable interest now in the potential of new drugs in development for the management of MDR-LTBI. The National Institutes of Health (NIH)-funded AIDS Clinical Trials Group has proposed a study of Tibotec's new adenosine triphosphate (ATP) synthase inhibitor bedaquiline in the treatment of MDR-LTBI in South Africa; however, despite promising indications of sterilizing ability[157] and tolerability[158] in therapy of active MDR-TB, concerns

Table 7 Treatment trials for latent tuberculosis infection: selected characteristics and outcomes

Author, year, reference no.	Year enrollmt began	Population	HIV	Number (active vs ctrl)	Rand-omized?	Location	Class	Active arm	Control	Freq	Result (active vs control; TB, or death if noted)	(S)AE	Percent complete	Comment
Egsmose 1965[34]	1959	HH contacts	N	325/301	Y by HH	Kenya	12H	12–24H	Placebo	Daily/daily	64% efficacy			
Comstock 1962[28]	1957	Native Alaskans	N	2,480/2,406	Y by family	Alaska	12H	12H	Placebo	Daily/daily	62% efficacy			
Del Castillo 1965[35]	1961	HH contacts re-cent cases	N	126/167	Y by family	Philippines	12H	12H	Placebo	Daily/daily	4% (42% in TST +)			
Ferebee 1962[31]	1957	HH contacts re-cent cases	N	8,478/8,311	Y by HH	USA,PR, Mexico	12H	12H	Placebo	Daily/daily	78% efficacy			
Ferebee 1963[29]	1957	Psychiatric pts	N	12,339/12,499	Y by ward	USA	12H	12H	Placebo	Daily/daily	64% efficacy			
Fitzgerald 2001[137]	1997	PPD-negative	Y	126/111	Y	Haiti	12H	12H	Placebo	Daily/daily	4.8%/3.6%-TB 15%/14%-death			23% LTFU
Thompson; IUAT Committee on Prophylaxis 1982[38]	1969	Fibrotic pulm lesions	N	6,919/6,990	Y	E. Europe	12H	12H	Placebo	Daily/daily	75% (all)-> 93% (cc) (5 year)	Hepatitis 0.64/ 0.12%	44/45	
Mount 1962[30]	1956	HH contacts known cases	N	1,462/1,348	Y by family	USA	12H	12H	Placebo	Daily/daily	54% efficacy			
Pape 1993[133]	1986	Adults, PPD positive	Y	58/60	Y	Haiti	12H	12H	Placebo	Daily/daily	2.2/7.5 per 100 py			
Veening 1968[36]	1960	Converting contacts	N	133/128	Y	Dutch Navy	12H	12H	Placebo	Daily/daily	92% efficacy			
Madhi 2012[169]	2004	Ped-infants	Y	273/274	Y	South Afr/ Botsw	12H	22H	Placebo	Daily/daily	11.4%/13.9%-TB 7.7%/5.5%-death	19.4%/14.2%	52/60	10–20 mg/kg/ d
Madhi 2012[170]	2004	Ped-infants	N	403/401	Y	South Afr/ Botsw	12H	22H	Placebo	Daily/daily	6.9%/7.7%-TB 0.5%/0.5%-death	6.2%/4.2%	81/81	10–20 mg/kg/ d
Falk 1978[37]	1964	Inactive TB	N	2,166/2,553/ 2,317	Y	USA	12H	24H/12H	Placebo	Daily/daily	60% if no prior therapy; else 0%	Death rates 4.0, 6.5, 4.4	73%	
Lincoln 1954[4]	1947/1952	Pediatric	N	129/421	N	NYC	12H	H added	STR,PAS, Sulfone	NS	1.5%/5.0%			
Pape 1993[133]	1986	PPD negative	Y	20/35	Y	Haiti	12H	12H	Placebo	Daily/daily	10%/14%-TB 10%/14%-death			No LTFU
Jasmer 2000[172]	1993	HIV-negative > 95%	’	477/545	N	USA	3–4HR	3–4HR	12H	Daily/daily	0.6%/1.1%	4.4/3.7	84/80	
Spyridis 2007[59]	1995	TST+ children < 15	N	694/232	Y	Greece	3–4HR	3–4HR	6H	Daily/daily	0%/0%	0/0	84/66	2 time peri-ods; 8% LTFU
Geijo 2007[58]	1996	Adults	N	51/45	Y	Spain	3–4HR	3HR	6H	Daily/daily	0%/2%	1.9/4.4	90/76	
Hong Kong Chest Service 1992[44]	1981	Silicotics	N	161/159	Y	Hong Kong	3–4HR	3HR	Placebo	Daily	22%/34%	29%/20%	76/84	TB at 5 years

(*Continued*)

Table 7 (*Continued*)

Author, year, reference no.	Year enrollmt began	Population	HIV	Number (active vs ctrl)	Rand-omized?	Location	Class	Active arm	Control	Freq	Result (active vs control; TB, or death if noted)	(S)AE	Percent complete	Comment
Martínez 1998[57]	1992	HIV-negative	N	98/98	Y	Spain	3–4HR	3HR	9H	Daily/daily	1.0%/0%	10%/20%	97/89	
Martínez 2000[60]	1994		Y	69/64	Y	Spain	3–4HR	3HR	12H	Daily/daily	2.9%/6.2%	7%/23%	63/57	
Martinson 2011[78]	2002	TST+ not on ART	Y	329/328	Y	South Africa	3–4HR	3HR	6H	TW/daily	7.3%/6.7%-TB 4.9%/7.6%-death	10.6/15.4	95/84	
Rivero 2003[62]	1994	Anergic	Y	82/77	Y	Spain	3–4HR	3HR	No rx	Daily/daily	3.7%/5.2%-TB 5%/14%-death	18%	84%	LTFU 13%
Rivero 2007[61]	1994	Adults	Y	103/108	Y	Spain	3–4HR	3HR	6H	Daily/daily	4.9%/3.7%-TB 0%/2%-death	6.8%/6.5%	61/64	LTFU 43%
Whalen 1997[63]	1993	TST+	Y	556/464	Y	Uganda	3–4HR	3HR	Placebo	Daily	1.6%/4.5%-TB 10%/14%-death	1.1%/0%	86/89	
Geiter 1997[173]	1988	Adults	N	132/131	Y	USA, Canada	3–4R	3–4R	6H	Daily/daily	NR	0%/1.5%	42/57	
Graczy 1991[175]	1988	HIV-negative	N	95/88	Y	Poland	3–4R	3–4R	6H	Daily/daily	0%/0%	2.1%/0%	91/68	
Hong Kong Chest Service 1992[44]	1981	Silicotics	N	165/159	Y	Hong Kong	3–4R	3R	Placebo	Daily	17%/34%	25%/20%	86/84	TB at 5 years
Lardizabal 2006[48]	2000, 2003	HIV-negative	N	261/213	N	USA	3–4R	4R	9H	Daily/daily	NR	3.1%/6.1%	81/53	
Menzies 2004[49]	2002	HIV-negative 99%	N	58/58	Y	Canada	3–4R	4R	9H	Daily/daily	NR	3/14	91/76	8% LTFU
Menzies 2008[50]	2004	HIV-negative 99%	N	420/427	Y	CAN, BRA, SA	3–4R	4R	9H	Daily/daily	NR	1.7/4.0	78/60	10% LTFU
Page 2006[45]	1999	HIV-negative 99%	N	1,379/770	N	USA	3–4R	4R	9H	Daily/daily	0.1%/0%	1.9%/4.6%	72/53	
Villarino 1997[43]	1993	INH-R; HIV-negative	N	157	N	USA	3–4R	6R	None	Daily	0%	0.60%	94	13% LTFU
Polesky 1996[42]	1984	INH-R; HIV-negative 95%	N	49/38	N	USA	3–4R	6R, 4HR	5H, None	Daily/daily	0%/8.3%	15%/11%	NR	TB: 33% HIV+ vs 7% HIV-neg
Martinson 2011[78]	2002	TST+ not on ART	Y	164/328	Y	South Africa	36H	36H	6H	Daily	4.9%/6.7%-TB 4.9%/7.6%-death	18.4/15.4	89/84	
Samandari 2011[143]	2004	Adults	Y	989/1006	Y	Botswana	36H	36H	6H	Daily/daily	2.0%/3.4%	2.9%/2.4%	78/79	
Thompson; IUAT Committee on Prophylaxis 1982[38]	1969	Fibrotic pulm lesions	N	6,956/6,990	Y	E. Europe	3H	3H	Placebo	Daily	21% (all)–> 31% (cc) (5 year)	Hepatitis 0.32/0.07%	95/97	Median age 50 years
Martinson 2011[78]	2002	TST + , not on ART	Y	329/328	Y	South Africa	3HP	3HP	6H	OW/daily	7.3%/6.7%-TB 5.2%/7.6%-death	8.7/15.4	96/84	
Schechter 2006[77]	2001	HIV negative 99%	N	206/193	Y	Brazil	3HP	3HP	2RZ	OW/daily	1.5%/0.5%-TB 0.5%/1.5%-death	1.9/14.0	93/94	2% LTFU

Table 7 (*Continued*)

Author, year, reference no.	Year enrollmt began	Population	HIV	Number (active vs ctrl)	Rand-omized?	Location	Class	Active arm	Control	Freq	Result (active vs control; TB, or death if noted)	(S)AE	Percent complete	Comment
Sterling 2011[79]	2001	HIV negative 97%	N	3,986/3,745	Y	US, BRA, SP, CA	3HP	3HP	9H	OW/daily	0.43%/0.19%-TB 0.8/1.0-death	1.6%/2.9%	82/69	
Whalen 1997[63]	1993	TST+	Y	462/464	Y	Uganda	3HRZ	3HRZ	Placebo	Daily	2.2%/4.5%-TB 13%/14%-death	2.8%/0%	80/89	
Hawken 1997[174]	1992	23% TST+ and 77% TST-	Y	342/342	Y	Kenya	6H	6H	Placebo	Daily/daily	7.3%/6.7%-TB 18%/17%-death	3.2%/1.5%	68/69	TB and mortality lower with INH if TST+
Gordin 1997[138]	1991	Anergic	Y	260/257	Y	USA	6H	6H	Placebo	Daily/daily	1.5%/2.3%-TB 50%/49%-death			7% LTFU
Hong Kong Chest Service 1992[44]	1981	Silicotics	N	167/159	Y	Hong Kong	6H	6H	Placebo	Daily/daily	20%/34%	25%/20%	74/84	TB at 5 years
Thompson; IUAT Committee on Prophylaxis 1982[38]	1969	Fibrotic pulm lesions	N	6,965/6,990	Y	E. Europe	6H	6H	Placebo	Daily	65% (all)-> 69% (cc) (5 year)	Hepatitis 0.48/0.32%	93/95	2.8% LTFU; INH hepatitis death rate 0.14/1,000
Mwinga 1998[68]	1992	TST+ or − Adults	Y	360/360	Y	Zambia	6H	6H	Placebo	TW/TW	13%/8%-TB 16%/16%-death	5.3%/1.4%	72/82	32% LTFU; signif.benefit only if TST $\geq$ 5 mm
Rivero 2003[62]	1994	Anergic	Y	83/77	Y	Spain	6H	6H	No rx	Daily/daily	3.6%/5.2%-TB 11%/14%-death	7%	78%	LTFU 18%
Whalen 1997[63]	1993	TST+ adults	Y	536/464	Y	Uganda	6H	6H	Placebo	Daily/daily	1.3%/4.5%-TB 11%/14%-death	0.7%/0%	88/89	
Whalen 1997[63]	1993	Anergic	Y	395/323	Y	Uganda	6H	6H	Placebo	Daily/daily	2.3%/3.1%-TB 22%/24%-death	0.5%/0%	86/85	
Zar 2007[171]	2003	Pediatric 0–4 year	Y	132/131	Y	South Africa	6H	6H	Placebo	Daily/3 wk	4%/10%-TB 8%/16%-death	4%/6.1%	NR	10 mg/kg/d or placebo, both with CTX
McNab 2000[170]	1992; 1986	Aboriginals	N	591/403	N	Canada	6HR	6HR	12H	TW/daily	0.3%/3.7%	6.6/2.2	82/19	Historical control group DOT vs SA
Geiter 1997[173]	1988	Adults	N	139/132	Y	USA, Canada	RZ	2RZ	6H	Daily/daily	NR	5.8%/1.5%	65/57	
Gordin 2000[70]	1991	PPD+ Adults	Y	791/792	Y	US, HA, MX, BRA	RZ	2RZ	12H	Daily/daily	3.5%/3.7%-TB 18%/20%-death	5.6%/7.3%	80/69	10% LTFU
Graczy 1991[175]	1988	Adults	N	106/88	Y	Poland	RZ	2RZ	6H	Daily/daily	0%/0%	2.8%/0%	91/68	
Halsey 1998[67]	1990	PPD+ Adults	Y	392/392	Y	Haiti	RZ	2RZ	6H	TW/TW	5.8%/3.8%-TB 18%/18%-death	0%/0%	74/55	11% LTFU
Jasmer 2003[167]	1999	Adults	N	307/682	Y	USA	RZ	2RZ	6H	Daily/daily	NR	7.7%/1.0%	61/57	Gr3–4 hepatotoxicity

(*Continued*)

Table 7 (*Continued*)

Author, year, reference no.	Year enrollmt began	Population	HIV	Number (active vs ctrl)	Rand-omized?	Location	Class	Active arm	Control	Freq	Result (active vs control; TB, or death if noted)	(S)AE	Percent complete	Comment
Leung 2003[165]	2000	Adult silicotics	N	40/36	Y	Hong Kong	RZ	2RZ	6H	Daily/daily	NR	35%/3%	55/64	
McNeill 2003[166]	1999	HIV-negative 98.5%	N	110/114	N	USA	RZ	2RZ	6H	Daily/daily	NR	13%/4%	71/59	
Narita 2002[168]	1999	Adults	Y	135/118	N	USA	RZ	2RZ	6H	Daily/daily	NR	3.7%/0%	93/63	D/C due to AE; 70% of RZ = RBT
Rivero 2003[62]	1994	Anergic	Y	77/77	Y	Spain	RZ	2RZ	No rx	Daily/daily	1.3%/5.2%-TB 6%/14%-death	17%	81%	LTFU 12%
Rivero 2007[61]	1994	Adults	Y	105/108	Y	Spain	RZ	2RZ	6H	Daily/daily	1.9%/3.7%-TB 0%/2%-death	11.4%/6.5%	60/64	LTFU 46%
Tortajada 2005[163]	2001	Adults	N	153/199	Y	Spain	RZ	2RZ	6H	Daily/daily	NR	9.8%/2.5%	71/73	Gr 3+ hepatotoxicity
Van Hest 2004[164]	2000	HIV-negative 99.8%	N	166/528	N	Holland	RZ	2RZ	6H	Daily/daily	NR	8.4%/3.4%	NR	Gr 3+ hepato-toxicity; 3.4% in 410 TB pts given HRZ+
Mwinga 1998[68]	1992–1994	TST+ or - Adults	Y	360/360	Y	Zambia	RZ	3RZ	Placebo	TW/TW	13%/7%-TB 19%/16%-death	4.4%/1.4%	79/82	32% LTFU; sig-nif.benefit only if TST $\geq$ 5 mm
Fitzgerald 2001[137]	1997	HIV+ after TB Rx	Y	68/74	Y	Haiti	SCC- > 12H	12H	Placebo	Daily/daily	1.4/100py vs 7.8/100 py			
Perriëns 1995[149]	1989–1991	Posttreatment	Y	123/124	Y	Zaire	SCC- > 6HR	6HR	No Rx	Daily/2 wk	1.9%/9% TB		60/70	

Abbreviations: AE, adverse event; CTX, cotrimoxazole; D/C, discontinued; DOT, directly observed therapy; H, isoniazid; HH, household; HIV, human immunodeficiency virus; INH, isoniazid; INHR, resistant to INH; LTFU, lost to follow-up; OW, once weekly; PPD, purified protein derivative; py, patient-year; R, rifampin; RBT, rifabutin; RZ, rifampin + PZA; SA, self-administered; (S)AE, serious adverse event; TST, tuberculin skin test; TW, twice weekly.

about the effect of this agent on QT prolongation or other as-yet inadequately characterized biochemical effects appear to have created reluctance to test these agents in healthy persons until a regulatory approval for use in active MDR-TB has been obtained. Similar interest and/or concerns have arisen with regard to other new agents, including delanamid (also known as OPC-67,683) and PA-824.[159]

Tumor Necrosis Factor-α Inhibitors

In 2001 Keane et al reported an association of aggressive TB and use of newer immunologic therapies directed against tumor necrosis factor (TNF).[160] Subsequent reports implicated different agents of this class (both monoclonal or fragmented antibodies, and soluble TNF receptors) with accelerated development of TB.[161] Multiple aspects of TB risk with TNF antagonist therapies were reviewed in 2010.[162] Reported rates of TB in persons receiving these agents were 10- to 100-fold greater than in the general population. In response, multiple and modestly discordant guidelines have been issued.[162] All advise testing for LTBI, and if positive, initiation of LTBI therapy at least 1 to 2 months before TNF antagonist therapy.

Future Directions

There is strong evidence that use of treatment for LTBI can prevent future TB cases in high-risk settings such as recent close contact to an active case (see ►**Table 7**[163–175] for a listing of LTBI treatment trials). Such treatment clearly prevents cases of TB, prevents deaths from TB, and thus provides benefit to some of the individuals treated. What is less clear is how this intervention can be applied in cost-effective ways. Recent investigations, including both clinical trials and epidemiological studies, suggest that some 50 to 70% of cases due to recent transmission have already occurred by the time current contact investigations identify and evaluate the individuals at risk.[176] This means that the "number needed to treat" is not 10 to 20 (if risk were 5 to 10%), but rather 40 to 67, which may have significant influence on the long-term impact of this strategy. Models that have favored use of LTBI treatment need to be reevaluated in light of this new information on efficiency.[177]

The discussion on use of TLTBI is also hindered by confusion between treatment of LTBI in low-prevalence settings and use of IPT in settings of high TB and HIV prevalence. In the latter setting, much of the benefit of IPT derives from (1) prevention of TB-related death, which occurs at higher rates in these settings, and (2) prevention of reinfection (which may be an important gain where TB transmission is intense, and a nonexistent gain in settings where it is not). Few studies to date have been able to make this distinction, and many trials of TB treatment are too small to distinguish reliably among these various outcomes. Moreover, there remains controversy about the role of testing for LTBI in high-prevalence settings. WHO policy makers recommend use of IPT for all HIV-infected persons in these settings, but most studies show little or no benefit accruing to those who are TST-negative. Other areas of uncertainty include the utility of rifabutin in treatment of LTBI, and the role of novel compounds in the prophylaxis of MDR-TB. Ongoing trials of INH-rifapentine regimens and of 4R will add to our understanding and increase the effective use of these important preventive therapies.

Disclaimer

The findings and conclusions in this review are those of the author and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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