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Treatment of latent tuberculosis infection: new cornerstones and new concerns

M. Elsa Villarino

Chief, Therapeutic and Diagnostic Studies Unit, Research and Evaluation Branch. Division of Tuberculosis Elimination. Centers for Disease Control and Prevention.

Correspondencia:
M. Elsa Villarino
Centers for Disease Control and Prevention
Atlanta, GA 30333
E-mail: MEV1@cdc.gov

Introduction

New recommendations entitled "Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection" were recently developed and published by a work group from the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC), with endorsement by the Infectious Diseases Society of America and the American Academy of Pediatrics[1]. Whenever possible, the recommendations were based on data from randomized clinical trials and other scientific evidence; otherwise, they were based on the expert opinion of the work group. As in other guidelines published by the CDC, this document includes an adaptation of the rating system used in other United States Public Health Service guidelines that grades the strength of the recommendation (A, B, or C) and the quality of evidence supporting the recommendations (I, II, or III).

In some countries such as the United States, diagnosing and treating of persons who have latent tuberculosis (TB) infection (LTBI) and a high risk for TB are essential components of the plan to eliminate TB[2]. For more than 30 years, the recommended management for LTBI has been a regimen of isoniazid taken daily for 6 to 12 months. However, the limitations of this therapy have been known for almost as long as it has existed, and are mostly due to the long duration of treatment that is required (resulting in poor medication adherence) and to concerns about toxicity. These problems prompted interest in developing shorter, rifampin-based regimens as alternatives to isoniazid for the treatment of LTBI. During the past decade, several clinical trials of "short-course" treatment of LTBI have been conducted among persons also infected with the human immunodeficiency virus (HIV). The results of these trials and the re-analyses of prior clinical trials of isoniazid are the scientific cornerstones of the new treatment recommendations[1].

Because identifying and diagnosing persons with LTBI correctly are critical first steps of an effective treatment program, updated recommendations on the tuberculin skin test (TST), which emphasize only testing persons at highest risk for TB, were also included in the new guidelines. This article will attempt to highlight the main components of the new recommendations, summarize the scientific deliberations that support them, and discuss some of the concerns that surround them.

Targeted tuberculin skin testing

The determination that a person has LTBI is a requisite for an effective treatment program. To encourage focused program activities, the term "targeted tuberculin skin testing" was adopted to replace the term "screening for TB". Targeted tuberculin skin testing means that the TST should only be used for persons at highest risk for TB. In the United States, analyses of epidemiological data have identified persons with increased risk for TB as those who a) have recent infection with *M. tuberculosis* or b) have clinical conditions that are associated with an increased risk for progression of LTBI to active TB[1].

Tuberculin testing programs should be targeted only to groups at risk for TB and discouraged for those at low risk. Based on the sensitivity and specificity of the purified protein derivative (PPD)-tuberculin skin test, the risk of developing TB if infected, and the prevalence of TB in different groups, three cut-points are recommended for defining a positive tuberculin reaction. For those who are at highest risk of developing active TB (i.e., HIV-infected persons or those receiving immunosuppressive therapy, recent close contacts of persons with infectious TB, or persons with abnormal chest radiographs consistent with prior TB), ≥5 mm of induration is considered positive. For

others with an increased probability of being recently infected or with other clinical conditions that increase the risk for progression to active TB, ≥10 mm of induration is considered positive. These include recent immigrants (who have been in the United States for <5 years) from high prevalence countries; injection drug users; residents and employees of high-risk congregate settings (including health care workers with exposure to TB); mycobacteriology laboratory personnel; persons with clinical conditions such as silicosis, diabetes mellitus, chronic renal failure, leukemias and lymphomas, carcinoma of the head or neck and lung, weight loss of ≥10% ideal body weight, gastrectomy, and jejunoileal bypass; and children <4 years of age or infants, children, and adolescents exposed to adults in high-risk categories. *Again, tuberculin skin testing is not indicated for groups* at low risk for TB. If for unavoidable or compulsory reasons a TST is done in these persons, then ≥15 mm of induration is considered positive.

Because only those at highest risk for TB should be tested, all persons who are diagnosed as infected should be offered treatment of LTBI, irrespective of age. Accordingly, the prior recommendation of using a cutoff age of 35 years to exclude candidates for treatment no longer applies. Persons at low risk for developing TB and who have had a TST for other reasons, such as health-care workers who have had a baseline TST, are not necessarily candidates for therapy if found to be infected (i.e., TST ≥15 mm). Similarly, for foreign-born persons from countries with a high prevalence of TB who have LTBI and who have been in the United States for ≥5 years, treatment decisions should be made on the same basis as for comparable persons without the foreign-birth risk factor.

BCG given through intracutaneous inoculation is currently used in many parts of the world as a vaccine against TB. Vaccination with BCG usually leads to the development of tuberculin reactivity, which wanes with the passage of time but can be boosted by the TST. There is no reliable method of distinguishing between tuberculin reactions caused by BCG vaccination and those caused by natural mycobacterial infections. It is sensible, therefore, to consider large reactions (for example, ≥15 mm) in BCG-vaccinated persons as indicating LTBI. Ideally, the cutoff for defining a significant reaction in BCG-vaccinated persons should be based on the analysis of local epidemiological data, such as TST survey results among BCG-vaccinated school children (to estimate the mean reaction size after vaccination). Often, however, this information is not available, in which case the arbitrary cutoffs of 10 or 15 mm must be used.

New recommended regimens for treatment of LTBI

The following recommendations are pertinent for adults who are likely to have LTBI with organisms susceptible to isoniazid and rifamycins. Several regimens for treatment of LTBI are currently recommended (Table 1).

Why 9 months of daily isoniazid?

A 9-month regimen of isoniazid taken daily is recommended because in subgroup analyses of several clinical trials in HIV-negative persons, the maximal beneficial effect of isoniazid was observed by 9 months, and minimal additional benefit is gained

Table 1. Recommended Drug Regimens for the Treatment of LTBI

Drugs	Duration	Interval	Rating* (Evidence)** HIV-	HIV+
Isoniazid	9 months	Daily	A (II)	A (II)
		Twice-weekly	B (II)	B (II)
Isoniazid	6 months	Daily	B (I)	C (I)
		Twice-weekly	B (II)	C (I)
Rifampin-Pyrazinamide	2 months or 2-3 months	Daily or Twice-weekly	B (II)	A(I)
			C (II)	C (I)
Rifampin	4 months	Daily	B (II)	B (III)

* A = Preferred, B = Acceptable alternative, C = Offer when A and B cannot be given. **I = Randomized clinical trial data, II = Data from clinical trials that are not randomized or were conducted in other populations, III = Expert opinion

by extending therapy to 12 months (AII)[3]. When compared with placebo, both 6-month and 12-month regimens are effective in HIV-positive patients; however, these regimens have not been compared with each other in randomized trials. It is possible that even longer courses of isoniazid are more effective treatment for HIV-infected persons, especially in high-TB incidence regions[4]. However, in the absence of such data, and to simplify the recommendations with a "unified" approach, isoniazid treatment for 9 months was also recommended for HIV-infected persons.

Although a 9-month regimen of isoniazid is the preferred regimen for the treatment of LTBI, a 6-month daily regimen also provides substantial protection and has been shown to be superior to placebo in both HIV-negative (BI) and HIV-positive persons (CI). In some situations, treatment for 6 months rather than 9 months may provide a more favorable outcome from a cost-effectiveness standpoint. Thus, based on local conditions, TB programs or clinicians may conclude that a 6-month rather than a 9-month course of isoniazid is preferred. Both the 9-month and 6-month isoniazid regimens may be given intermittently (i.e., twice weekly). The 6-month intermittent regimen is rated BII for HIV–negative and CI for HIV-positive persons. When isoniazid is given intermittently, it should be administered only as directly observed therapy (DOT).

Why short-course multidrug regimens?

The 2-month daily regimen of rifampin and pyrazinamide (2RZ) is recommended on the basis of a prospective randomized clinical trial of treating of LTBI in HIV-infected persons (AI)[6]. The trial showed the 2-month regimen to be similar in safety and efficacy to a 12-month regimen of isoniazid (incidence of TB was 0.8% for the RZ group vs 1.1% for the isoniazid group). Although there are no efficacy data from controlled trials on the use of rifampin and pyrazinamide treatment for HIV-infected patients, there was a consensus that this regimen would be effective for immunocompetent persons (BII).

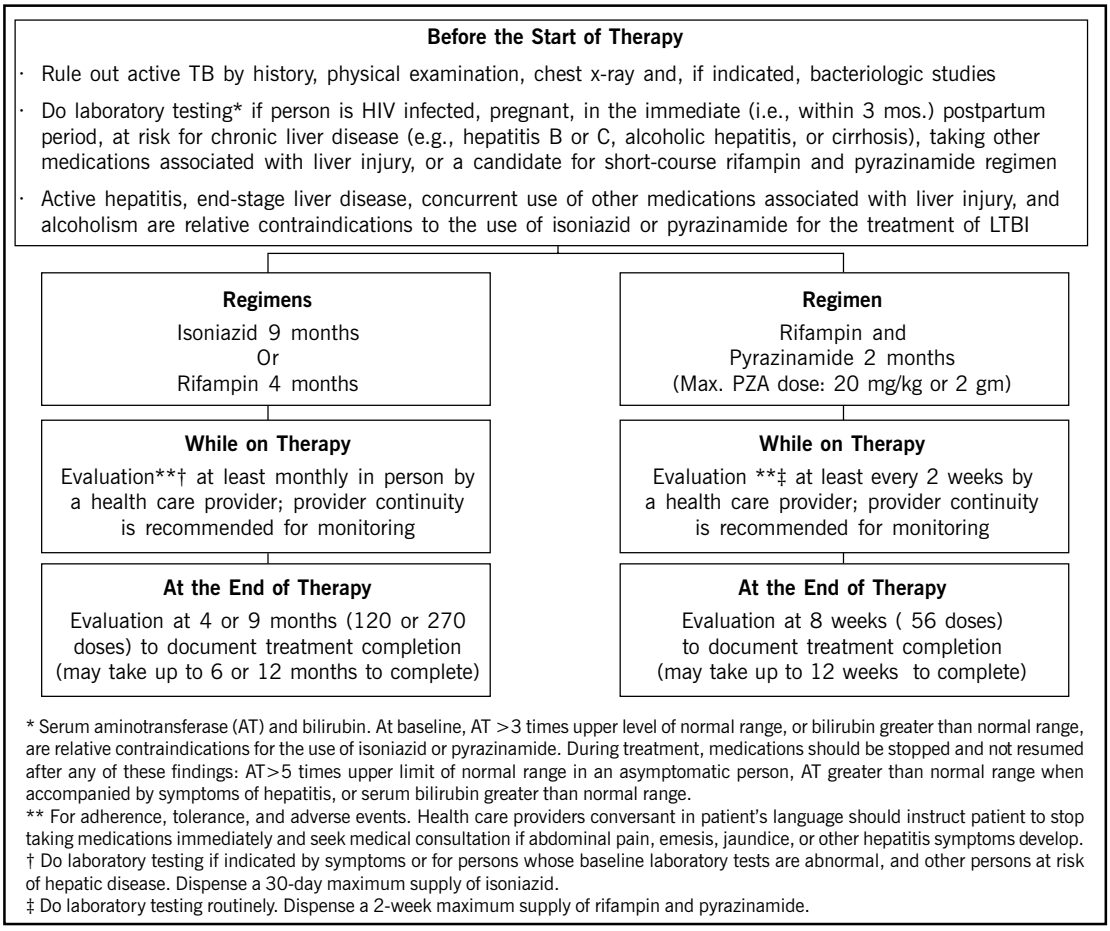
After much debate, the efficacy data from two trials that evaluated twice-weekly treatment with RZ for 2 and 3 months were considered inconclusive, because the sample sizes were small and the comparison treatment arms consisted of isoniazid given only for 6 months[7,8]. Therefore, twice-weekly RZ was recommended only for situations in which alternative regimens cannot be given (CI). This intermittent regimen should always be administered as DOT. Some experts recommend that the 2-month regimen of daily rifampin and pyrazinamide also be given by DOT, which can consist of five observed and two self-administered doses each week. In situations in which rifampin cannot be used (e.g., HIV-infected persons receiving protease inhibitors), rifabutin may be substituted[9]. Rifampin given daily for 4 months is recommended on the basis of the efficacy of a similar regimen in a prospective randomized trial of tuberculin-positive persons with silicosis[10] as well as in a nonrandomized trial in persons exposed to isoniazid-resistant TB[11] (BII for HIV-negative and BIII for HIV-positive persons). This option may be especially useful for patients who cannot tolerate isoniazid or pyrazinamide.

Another multidrug regimen that was not included in the new recommendations[1] but that is utilized in clinical practice and has been included in randomized clinical trials is isoniazid and rifampin used together for 3 months[4,5]. This regimen is comprised of two drugs with strong sterilizing capacity and activity against intermittently metabolically active and intracellular organisms, and in the setting of impaired cell mediated immunity caused by HIV infection, may play an important role in determining the long-term outcome of treatment of LTBI. In a large clinical trial in Uganda[4,5], a regimen of 6 months of isoniazid initially protected against TB in TST-positive individuals; however, the benefit was lost within the first year of treatment. In contrast, sustained protection for up to 3 years was observed in patients receiving 3 months of isoniazid and rifampin or 3 months of isoniazid, rifampin, and pyrazinamide. When these two rifampin-containing regimens were combined in analysis, the adjusted protection against TB compared with placebo was 54% and statistically significant.

Clinical and laboratory monitoring before and during LTBI therapy

Whenever LTBI is suspected in a patient, an evaluation should be conducted to rule out active TB and assess the appropriateness of LTBI therapy (Figure 1). This evaluation should include HIV counseling and testing for persons whose HIV status in unknown but who are at risk for HIV infection. The major departure from prior guidelines is a shift to clinical instead of routine laboratory monitoring for most patients, with the exception of HIV-infected patients, women who are pregnant or in the

Figure 1. Clinical and Laboratory Evaluation for Patients Who Are Potential Candidates for Latent TB Infection (LTBI) Therapy



immediate postpartum period, persons at risk for chronic liver disease, and persons undergoing LTBI therapy with regimens other than isoniazid or with rifampin alone.

Concerns about LTBI therapy intolerance and liver function abnormalities

The recommendation to emphasize clinical instead of routine laboratory monitoring for most patients during treatment for LTBI is based in part on a survey showing that many public health departments now use clinical instead of biochemical monitoring for hepatotoxicity[12]. Clinical monitoring necessitates educating patients about symptoms of liver dysfunction and instructing them to stop treatment if such symptoms occur and to report for further evaluation. After using clinical monitoring exclusively one public health TB clinic reported only 11 cases of clinical hepatotoxicity and no deaths among >11,000 persons with LTBI who were treated with isoniazid over a 7-year period[13].

Available data also did not suggest excessive risk for severe hepatitis associated with 2RZ treatment among HIV-infected persons. In a large multinational trial, HIV-infected patients treated with 2RZ had lower rates of serum aminotransferase (AT) elevations than those given isoniazid alone[6]. The 2RZ regimen also was well tolerated when given twice weekly to HIV-infected persons in Zambia and Haiti [7,8]. However, the rates of drug discontinuation and elevations in AT levels were higher in pilot studies[14,15] of rifampin and pyrazinamide treatment of HIV-uninfected patients (about 26%) than in clinical trials including HIV-infected patients (about 12%)[6-8]. Therefore, the guidelines committee concluded that the spectrum of possible toxicity for rifampin and

pyrazinamide, especially in HIV-uninfected persons, was not yet fully understood, and that for field implementation of the 2RZ regimen the recommendation for clinical monitoring alone would not be sufficient.

Since the publication of the guidelines in May 1999, reports of toxicity due to 2RZ continue to be contradictory. After monitoring monthly, 1 jail system that treated 168 inmates (166 or >99% HIV-negative at time of incarceration) with 2RZ reported stopping treatment in only one inmate (<1%) for asymptomatic elevation of asparginine aminotransferase (≥10 times normal), in 12 inmates (7%) for minor complaints, and no deaths due to 2RZ[16]. However, there have been also two reports published on fatal and sever liver injuries associated with rifampin and pyrazinamide for LTBI[17,18]. The first report, dated April 20, 2001, described two cases of hepatitis, one fatal and one severe. These cases had two common denominators: 1) biochemical monitoring was done as recommended but did not prevent severe hepatitis and 2) both patients continued therapy while symptoms developed. Each patient also had a potential cofactor for liver injury (alcoholism and drug-induced hypersensitivity, respectively). A passive surveillance system was begun as a result of this publication to include all cases of severe liver injury that results in admission to a hospital or death in patients treated with 2RZ and reported to the CDC. The characteristics and outcomes of 21 of these patients were summarized in a second report, dated August 30, 2001[18]. Among these 21 patients the median age was 44 years (range 28-73) and 12 were men. There was no known HIV infection among 11 tested, and about one third had positive serologies for viral hepatitis but none had evidence of acute infection. The median age of the five fatal cases was 36 years (range 32-68) and three were men. There was no known HIV infection, and two had a positive serologies for viral hepatitis infection; none had evidence of acute infection. All five patients had onset of liver injury during the second month of treatment and some continued with therapy after symptoms developed (four received 30-day supplies of rifampin and pyrazinamide), two were taking other medicines associated with idiosyncratic liver injury, one developed symptoms at the completion of therapy, and one received DOT daily but communication about symptoms was apparently impaired by a language barrier.

There are several limitations to the analyses and interpretation of the passive liver injury surveillance system. The most important of these limitations is the absence of denominator data and therefore the inability to calculate hepatotoxicity and mortality rates associated with 2RZ. The toxicity associated with this regimen therefore cannot be adequately compared with the toxicity of using isoniazid alone for LTBI therapy. In addition, this system cannot quantify differences in the quality of medical care received by patients treated with rifampin and pyrazinamide, nor can it determine the mechanism(s) of 2RZ liver toxicity. Nonetheless, the occurrence of these events prompted revised recommendations regarding the use of the 2RZ regimen[18]. These revised recommendations supercede the previous guidelines[1] and are included in the Figure. In particular, these new guidelines emphasize the following:

a. 2RZ should be used with caution, especially in patients taking other medications associated with liver injury and in those with alcoholism;
b. 2RZ is not recommended for those who have had INH-associated liver injury;
c. patients should be dispensed a 2-week maximum supply of medications;
d. the PZA dose should be limited to <20 mg/kg/d or 2 gm maximum;
e. patients should always be followed-up in person, and serum AT and bilirubin measurements should be done at baseline, 2, 4, and 6 weeks during treatment, with an additional 8-week visit to document treatment completion;
f. patient education should be done in the patient's language at each visit; and
g. therapy should be stopped immediately if hepatotoxicity symptoms are reported, if AT levels rise to >5 times the upper level of normal in an asymptomatic person, if AT levels are in the greater-than-normal range when accompanied by symptoms of hepatitis, or if serum bilirubin levels rise to the greater-than-normal range.

Conclusion

With a greater choice of treatment regimens for LTBI, there is also a greater opportunity to prevent new cases of TB. At the same time, the occurrence of cases of severe hepatoxicity resulting in liver transplantation or death in patients treated for LTBI has negative consequences for a community and for a TB control program. The final recommendations are intended to provide a balance between these issues. They are intended to facilitate the implementation of the 2RZ regimen in field conditions, with a cautious approach for persons at risk of unwanted and serious adverse events due to this intervention.

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