

Comments on Recent Guidelines for the Treatment of Tuberculosis by the American Thoracic Society, the Centers for Disease Control and Prevention, and the Infectious Diseases Society of America

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The American Thoracic Society (ATS) has just published extensive guidelines on the treatment of tuberculosis (TB).¹ The document has many positive aspects but others that can be questioned or even criticized. Perhaps the first point in its favor is the fact that these recommendations, which take levels of evidence into consideration, have been accepted and approved by the Centers for Disease Control and Prevention (CDC) and the Infectious Diseases Society of America (IDSA), making it the document on the treatment of TB most widely accepted by the scientific societies of the United States. Another favorable aspect to mention is that the purpose of the guidelines is highlighted on the first page of the document, in a box under the table of contents, making it clear that they should be followed by countries with substantial economic resources. This is very important and has not been stated in previous ATS guidelines, causing the vast majority of private medical specialists in countries with scarce or middling economic resources (which bear the burden of 95% of the world's TB cases) to regard the guidelines as the procedures to follow without adapting them to local economic and epidemiologic situations, even when recommendations were inconsistent with those of their own national TB control programs. The measures to be adopted for the treatment and control of TB in rich countries, and for which these recommendations of the ATS are perfectly valid, are quite different from those of poor countries which should follow the guidelines of the World Health Organization² and the International Union against Tuberculosis and Lung Diseases.^{3,4} Although aspects of treatments may be similar for both "worlds," methods of diagnosis, follow up, and control have very different protocols. The first point to underline, then, is that these

guidelines are only valid for 5% of the world's TB sufferers, those that come from developed countries, Spain included.

Perhaps the first two comments to make about this document should refer to its length (60 pages of the journal) and the range of treatments recommended: although the best treatment regimen is recognized to be 6 months long (2 months with isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 4 months with isoniazid and rifampicin) administered daily or intermittently, many different therapeutic strategies are recommended. Consensus documents and official recommendations of scientific societies should be brief and concise to encourage their being read by the largest possible number of people concerned, thereby increasing their impact. Detailed explanations on each and every point can be left to the manuals and treatises of the same scientific societies.⁴ Furthermore, if a therapeutic strategy is accepted as optimal, in certain circumstances recommending others can only generate confusion, possible mistakes and, above all, improvisations by some practitioners, a situation that can lead to increased resistance to the drugs.⁴

The ATS recommendations introduce certain radical changes, 4 of which deserve special attention both for being new and, in some cases, questionable. The 4 changes are detailed below:

1. Treatment that includes the administration of isoniazid and rifampine once a week for 4 months in the second phase, in human immunodeficiency virus seronegative patients with noncavitary chest radiographs and who have negative sputum smears at the end of the second month of treatment. This recommendation is based on 2 fine studies by the CDC^{5,6} which found, however, a high relapse rate with single drug resistance to rifamycin in human immunodeficiency virus seropositive patients.⁶ This once-weekly treatment did not prove to be more efficacious than the 6-month

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treatment with rifampicin in 2 phases (2 months with isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 4 months with isoniazid and rifampicin), so the only advantage is that it allows medication intake to be supervised in the second phase. The disadvantages, however, include making the overall treatment of TB patients more complicated and the cost much higher. Moreover, rifapentine is difficult to obtain and strict supervision of administration is absolutely essential to assure patients do not miss a single dose of medication.

2. The recommendation to prolong treatment to 9 months with isoniazid and rifampicin (2 months with isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 7 months with isoniazid and rifampicin), in patients who fulfill 2 conditions: cavitary radiography at the start of treatment and positive sputum smear at completion of 2 months of treatment. This recommendation was also based on a study by the CDC,⁵ as a consequence of the over 20% relapse rate in patients who fulfilled these 2 conditions and had been treated with the 6-month isoniazid regimen. Patients who had only one of the conditions had relapse rates of under 5% and those with neither condition, less than 2%. Despite the validity of this study,⁵ it does not demonstrate that the high relapse rate is corrected with the extension of the treatment to 9 months.

3. The possibility of suspending the treatment after 4 months completion in patients classified clinically and radiographically as having TB but whose sputum smear and culture are negative. If there is a clinical improvement in these patients by the end of the second month and the initial culture is confirmed as negative, the 2 months with isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 2 months with isoniazid and rifampicin regimen is recommended, as it was recommended as an alternative for inactive residual TB in the 1994 official ATS guidelines.⁷

4. Treatment with 4 to 6 second line drugs is recommended for patients who are carriers of strains resistant to isoniazid and rifampicin (multi-drug resistant [MDR]) and other first line drugs. This significant, controversial change in the handling of these complicated cases is apparently based on 3 studies⁸⁻¹⁰ in which better results were obtained using the increased number of drugs. However, on careful revision of the 3 studies, it is surprising to find that none of them compares treatment regimens or demonstrates that the increased number of drugs led to better results in the treatment of these patients. Thus important changes have been recommended based on 3 references that do not demonstrate that the changes are justified. The first reference is the study carried out by Goble et al⁸ at the Department of Medicine, National Jewish Center for Immunology and Respiratory Medicine, Denver (Colorado, USA), who published the results of treating 171 patients who were resistant to an

average of 6 drugs including isoniazid and rifampin. Of the 134 patients that could be followed up, 87 (65%) responded to the treatment administered and 47 (35%) had no response. In the authors' univariate analysis, an unfavorable response was associated with 4 factors: prior administration of a larger number of drugs, treatment regimens with fewer drugs not used previously, resistance *in vitro* to a greater number of drugs, and male sex; however, only the first and last were statistically significant in a multivariate analysis. The second reference is the study by Park et al⁹ on the results of treating 107 Korean patients resistant to an average of 4 drugs including isoniazid and rifampin. There was sufficient follow up in 63 cases: 52 (82.5%) responded to treatment and 11 (17.5%) had no response. Univariate analysis showed that the only factor that was significantly associated with an unfavorable response was resistance to a greater number of drugs *in vitro*, and that factor continued to be significant in the logistic regression model. Finally, the third reference is the study carried out in the Netherlands by Geerligts et al,¹⁰ on the treatment of 44 patients with resistance to an average of 5 drugs including isoniazid and rifampicin. However, only 3 of the 44 patients were resistant to 5 drugs considered to be first line. The patients were treated with an average of 6 drugs including isoniazid in 36 cases despite the patients' proven resistance. The results were that 33 patients (75%) were cured, 6 (14%) died (only 1 from TB), and the rest were being followed up. No statistical analysis was made in this study to relate good or bad responses to particular factors.

Thus none of the 3 articles concluded that the use of 4 to 6 drugs was associated with better results.¹ Indeed, the only conclusion that can be drawn is that in these 3 studies acceptable results were obtained using more than 4 drugs, with favorable responses that oscillate between 65%⁸ and 82.5%.⁹ However, it should be remembered that in the 1950's and 1960's, before the discovery of rifampicin, many studies on patients resistant to isoniazid and streptomycin, among other drugs, were published that had very good results using only 3 drugs.¹¹⁻¹⁶ Many of these studies predated ethambutol, which means that treatment of these patients was just as complex as the MDR cases today that were analyzed in the articles mentioned.⁸⁻¹⁰

This unsupported change in the ATS guidelines for the treatment of these patients is remarkable in that the official guidelines of 1965¹⁷ and 1966¹⁸ recommended the use of only 2 or 3 new drugs in these cases. There was a certain shift in the 1994 guidelines,⁷ where the use of at least 3 new drugs was recommended, without any references that justified the change. The administration of 4, 6, or more drugs, apart from not being bacteriologically justifiable, insures a high probability of intolerance on the part of the patient, who

will abandon treatment or demand that medication be suspended when serious adverse reactions occur.

There are two further comments to be made on the guidelines analyzed here. The first concerns the recommendation to use ethambutol on all initial patients as a fourth first line drug. This was included in the 1994 guidelines,⁷ clearly contradicting the 1986 guidelines¹⁹ which had recommended the use of only 3 drugs in the initial phase. The change in the 1994 guidelines was due to the increase in the rate of initial resistance to isoniazid that had been observed in the United States. There is no explanation given for continuing to use the fourth drug in the current guidelines. As regards Spain, there has been no national study carried out on resistances to antituberculosis drugs but the results that have been gathered in different regions of the country²⁰⁻²² indicate a low rate of initial resistance to isoniazid. This means that use of ethambutol in the first phase is not justified in Spain, except maybe in the cases of immigrants who come from areas where TB is highly endemic and of other groups at risk of being carriers of resistant strains.

The second comment concerns extrapulmonary TB, which is thoroughly analyzed in the document; the same 6-month treatment (2 months with isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 4 months with isoniazid and rifampicin) as for pulmonary TB is recommended except in the case of meningeal TB where the recommended treatment is extended to 9 to 12 months.¹ Although there are no randomized controlled trials that compare the 6-month treatment with longer ones in the treatment of meningeal TB, there are trials that demonstrate the validity of the 6-month regimen,²³ so, in order to simplify and standardize the treatment of all forms of TB, it might be better to recommend the 6-month regimen for the treatment of meningeal TB.

To conclude these comments and criticisms on the fine recommendations for TB treatment issued by the ATS/CDC/IDSA,¹ this author believes that all initial forms of TB should be treated with the same 6-month regimen, which in Spain should not include ethambutol in the first phase (2 months with isoniazid, rifampicin, and pyrazinamide, followed by 4 months with isoniazid and rifampicin). Moreover, patients who are carriers of MDR strains should have a retreatment schedule of only 3 drugs that they have never received and to which they are susceptible.

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