

EDITORIALS



Practical Preventive Therapy for Tuberculosis?

Christopher Dye, D.Phil., F.Med.Sci.

Every new episode of tuberculosis — there were 9 million in 2010¹ — follows a period of asymptomatic infection lasting from weeks to decades. These subclinical infections, which are detectable with a tuberculin skin test or interferon- γ release assay, offer a target for prophylactic treatment either with drugs or, potentially, a vaccine. Vaccination after infection is not yet an option, but drug treatment has been available for 60 years in the form of 6 to 12 months of isoniazid preventive therapy (IPT), which protects up to 90% of infected persons from active tuberculosis. And yet very few tuberculosis-control programs have successfully carried out IPT on a large scale or even as a targeted treatment for persons at especially high risk for tuberculosis, such as children, contacts of persons with infectious cases, patients with human immunodeficiency virus (HIV) infection, or migrants from countries in which tuberculosis is highly endemic.

The limited success of IPT is due to a combination of the patients' choice and public-health priorities. Infected but asymptomatic persons who have a small chance of progressing to active tuberculosis are often resistant to taking a drug every day for up to 12 months, risking hepatitis and other side effects. Operationally, program managers know that it would be hard to ensure adherence to the lengthy treatment regimen. Furthermore, IPT is less cost-effective than treating patients with active tuberculosis. The reason is that although isoniazid is cheap, hundreds of infected persons must be treated to prevent one case of tuberculosis.²

Chemotherapy for active tuberculosis, the principal control strategy today, is comparatively cost-effective but far from ideal. At the patient level, we wait for infections to progress to a potentially

fatal, infectious illness for which treatment is not always successful. At the population level, the rate of reduction in the incidence of tuberculosis under chemotherapy is constrained by long periods of latency. Even in the best control programs, in which infection is diagnosed early and with high cure rates, it is not feasible to cut the incidence of tuberculosis by more than about 10% per year. Present evidence suggests that the control programs now operating in most high-burden countries, despite successes in elevating cure rates and reducing mortality, are achieving much less than 10% per year.¹ To compound the problem, as the incidence of tuberculosis falls, the rate of decline slows because growing numbers of cases are developing from old infections. The upshot is that a direct attack on latent infection will be needed before we can think about the elimination of tuberculosis.³

The latest in a series of investigations of shorter preventive regimens^{4,5} is presented in this issue of the *Journal*. Sterling et al.⁶ carried out a randomized trial of the efficacy of 3 months of isoniazid plus rifapentine combination therapy, given once a week under supervision, as compared with 9 months of daily, self-administered isoniazid alone. This was a noninferiority trial because the efficacy of isoniazid alone in preventing active tuberculosis is already high; the main question was whether efficacy and effectiveness would be at least as good with the shorter, more easily supervised regimen.

Because the study evaluated high-efficacy treatments in four low-incidence countries (Brazil, Canada, Spain, and the United States), there were few cases in either of the two well-matched groups in the trial. During 33 months of follow-up in 7731 subjects, an intention-to-treat effec-

tiveness analysis counted 7 cases of tuberculosis in the combination-therapy group and 15 in the isoniazid-only group, for cumulative incidence rates of 0.19% and 0.43%, respectively, and a hazard ratio of 0.38 (95% confidence interval, 0.15 to 0.99). Because intention-to-treat analysis confounds adherence with therapeutic efficacy (better adherence was expected and observed in the shorter, supervised combination-therapy group), Sterling et al. rightly present a per-protocol efficacy analysis, inevitably yielding a smaller difference between the two study groups. However, both analyses showed that combination therapy tended to be superior to isoniazid alone and was clearly not inferior. In the combination-therapy group, fewer patients had hepatotoxicity, as expected from the lower total dose of isoniazid, but hypersensitivity was more commonly associated with the combination of isoniazid plus rifapentine.

The findings of this trial, performed in low-incidence countries, suggest that isoniazid plus rifapentine is as good as the principal competing regimens — notably, 3 months of isoniazid plus rifampin or 4 months of rifampin monotherapy in places where the use of isoniazid is not recommended. However, a head-to-head comparison of these three options remains to be performed.

Preventive therapy has the potential to deliver greater health benefits in high-incidence countries. In this context, a critical question for the isoniazid-plus-rifapentine regimen is whether 3 months of treatment will provide protection for longer than 2 to 3 years. Evidence from other studies has suggested that it might be adequate for HIV-negative persons but not for those with HIV infection. In a population of Alaskan Inuit living under intense transmission of tuberculo-

sis (before the HIV era), a course of IPT was strongly protective for at least a decade.⁷ In contrast, recent studies of HIV-positive patients in Botswana⁸ and South Africa⁵ have reinforced the earlier finding that the incidence of tuberculosis increases soon after the discontinuation of IPT. In Botswana, the incidence of tuberculosis was more than 10% per year soon after the discontinuation of IPT, presumably because of the reactivation of residual infection, supplemented by reinfection. Would combination therapy with isoniazid plus rifapentine have to be given continuously and under supervision to protect HIV-positive or HIV-negative persons from reactivation or reinfection? A long-term study in a high-incidence setting is needed to find out.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Department of Zoology, University of Oxford, Oxford, United Kingdom.

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Inflammation in Multiple Sclerosis — Sorting Out the Gray Matter

Peter A. Calabresi, M.D.

In this issue of the *Journal*, Lucchinetti and colleagues report a high prevalence of cortical gray-matter inflammation and demyelination on tissue obtained at biopsy from patients with multiple sclerosis of new onset.¹ Although several

prior studies have documented demyelinating lesions in the gray matter of persons with multiple sclerosis,^{2,3} none of these investigations analyzed tissues from more than one newly diagnosed patient. The findings of the study by Lucchinetti