EDITORIALS

Facing Extensively Drug-Resistant Tuberculosis — A Hope and a Challenge

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As of June 2008, a total of 49 countries worldwide reported to the World Health Organization (WHO) at least one case of extensively drug-resistant tuberculosis. Since its first description in March 2006,[1] this disease has become the most alarming issue in international tuberculosis control and one that seriously risks compromising the progress observed in many countries over the past decade.[2] Extensively drug-resistant tuberculosis, which is especially frequent among drug-resistant cases in the former Soviet Union, has been linked with very poor treatment outcomes and deemed potentially untreatable in both developing and rich countries.[3]

Initial evidence has come from observations among patients coinfected with the human immunodeficiency virus (HIV) in South Africa, where extensively drug-resistant tuberculosis has been fatal in virtually all cases.[4] But evidence has also come from studies of mostly HIV-seronegative patients in Europe, the United States, and Korea,[5-7] where extensively drug-resistant tuberculosis was associated with much higher failure and mortality rates than multidrug-resistant tuberculosis (see the letter "Treatment Outcomes in Extensively Resistant Tuberculosis" in this issue of the *Journal*). The report from metropolitan Lima, Peru, published in this issue of the *Journal*, however, reveals a new and brighter perspective: even in developing countries, extensively drug-resistant tuberculosis may be cured in the majority of cases when management is aggressive and appropriate.[8] In this study, 60% of the patients with extensively drug-resistant tuberculosis completed treatment successfully, a percentage similar to that of patients in the same study with multidrug-resistant tuberculosis. This encouraging result constitutes a true change in the current perception of the disease as a virtual death sentence.

Because of this unexpected success, it is tempting to try to identify systematic biases in the study. For instance, the retrospective study design is such that the denominator is unknown and the patients referred to the treatment centers in metropolitan Lima could be the less sick, the most likely to survive, and the more likely to adhere to treatment. In fact, this study was not a large-scale, prospective, controlled intervention. Furthermore, one could speculate that drug-susceptibility testing for some of the second-line drugs was hampered by standardization problems[9]; thus, the results could be not entirely correct.

These points notwithstanding, one should focus on the factors that might have contributed to such a high level of treatment success among patients with extensively drug-resistant tuberculosis in a low-income country. These patients, whose previous treatment had failed or who had relapsed, were all at high risk for drug resistance. Thus, all patients underwent systematic drug-susceptibility testing, and while they awaited results and potential adjustments of treatment regimens, therapy with at least five (presumably effective) drugs was begun. In all cases, the regimens contained the most powerful second-line agents: a fluoroquinolone and an injectable drug. When regimens seemed to fail, and once drug-susceptibility testing results became available, the regimens were reinforced with the addition of known effective drugs and other secondary agents. The use of the injectable drug was prolonged for up to 15 months, the overall treat-

ment lasted the required 2 years, and a few seriously ill patients were referred for surgery. This is an aggressive approach, and it would be interesting to know the frequency and seriousness of the side effects. Yet the results suggest that side effects were probably well managed; defaulting was minimal, and definitive suspension of treatment was not reported.

Furthermore, strict treatment supervision was enforced. This is essential in managing tuberculosis, particularly when second-line drugs are used; creating additional drug resistance will exacerbate an already catastrophic situation in the individual patient while creating the basis for dissemination in the community. However, supervision did not consist of merely watching people follow regimens; it had all the elements of support for successful long-term treatment: it was community-based in the majority of patients, thus avoiding the additional stress of prolonged hospitalizations; it included psychological support for people taking potentially toxic drugs; and it included nutritional support and financial incentives, when needed. Finally, bacteriologic and clinical monitoring was intense, allowing readjustments and optimization of the case-management approach.

All these elements are crucial to success in tuberculosis control in general and in the management of severely drug-resistant cases in particular. They are all part of the Stop TB Strategy promoted by the WHO[10] and have been incorporated in recent international programmatic and care guidelines for drug-resistant cases.[11,12] If every national program put this strategy in place with equal vigor and assertiveness, as in the metropolitan Lima project, drug resistance would be minimized and, when already present, effectively managed.

Why is it that such high rates of cure and low rates of fatality have not been achieved by tuberculosis programs elsewhere, including programs in the United States and Europe that specialize in the management of drug-resistant tuberculosis?[5,6] The series reported so far from resource-rich countries may have included more severely, even terminally, ill patients. Possibly, the strains causing their disease were resistant to more drugs than the strains in Peru. For instance, the series reported from Italy included some patients affected by a form of extensively drug-resistant tuberculosis that was resistant to all available drugs.[5] Or perhaps the individual care was not as rigorous as that provided in metropolitan Lima. In particular, supervision of treatment and patient support may not have been of the same quality, especially for the patients in the European study.[5] Also, one cannot exclude the point that the Lima project enjoys a certain "exceptionality" bias. The project setting partly coincides with that of an exceptional site in northern Lima that has shown remarkable results among multidrug-resistant tuberculosis patients, with cure rates above 70%.[13] The recipe for that project included a strong partnership shared by a local nongovernmental organization (NGO) that implemented care, a U.S.-based NGO providing expertise and financial resources, and the Ministry of Health of Peru. Such partnership has established local capacity and a level of expertise that is rarely found elsewhere. These new observations[8] suggest that the model also works when used to address the most difficult challenge of tuberculosis control today, although further increases in cure rates could be achieved by perfecting the use of current tools and rapidly implementing new ones as they become available.

Can this model be scaled up to cover the entire country, and can it be replicated in other countries with different economic and social conditions? How can a rigorous approach to a high standard of individual care be expanded to a programmatic scale and become routine public health practice? In 2008, scaling up is indeed the major challenge faced by most complex health interventions worldwide, especially when health systems and services are not optimal.[14] What is required is action that is borne out of clear planning, financial commitment and adequate resources, technical capacity, and partnership. Ultimately, the effectiveness of a complex intervention depends on coordinated work among all forces. The Peru experience is a clear example that, in this spirit, even the most difficult objectives can be reached. The challenge is to make this approach a sustainable reality worldwide.

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Monoclonal B-Cell Lymphocytosis — A Frequent Premalignant Condition

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Chronic lymphocytic leukemia (CLL), a lymphoproliferative disorder of B cells, is the commonest form of leukemia in Western countries, with an incidence of 6 cases per 100,000 persons in North America[1]; since most cases are discovered through an incidental blood count, the prevalence of the disease may be even higher. The median age at diagnosis and at death was 70 and 76 years, respectively, among men and 74 and 81 years, respectively, among women. First-degree relatives of patients are three times more likely than members of the general population to have CLL or another lymphoid neoplasm.[2]

CLL has a variable course — survival ranges from months to decades. One third of patients never require treatment and have a long survival; in another third, an initial indolent phase is followed by disease progression and a requirement for treatment; the remaining third have an aggressive form of CLL at the onset and need immediate treatment.[3] The Rai[4] and Binet[5] staging systems, based on the extent of the disease and the presence of anemia, thrombocytopenia, or both, allow for the classification of patients into three groups with a good prognosis (Binet stage A, Rai stages 0 and 1), intermediate prognosis (Binet stage B, Rai stage 2), or poor prognosis (Binet stage C, Rai stages 3 and 4). These staging systems have been the basis of the design of clinical trials, but neither can predict the development of progressive disease in patients characterized as having a good prognosis.[3,6] In Western countries, 75% of all patients with CLL fall into this group.

There are, however, molecular and cellular markers that can help to predict the tendency toward disease progression. One important molecular marker is the status of immunoglobulin heavy variable group (*IGHV*) genes in the CLL cells. Patients in whom these genes are not mutated (germ-line) have a worse prognosis than patients in whom the CLL cells harbor mutated *IGHV* genes.[7,8] A poor prognosis is also associated with the presence in CLL B cells of a genetic lesion at chromosome 17p13 (the site of the tumor protein p53 [*TP53*] tumor-suppressor gene) or at 11q23 (the site of the ataxia–telangiectasia mutated [*ATM*] gene). Some cytotoxic drugs used for the treatment of CLL disrupt DNA and require an intact p53 protein to eliminate cells with damaged DNA. The 17p13 and 11q23 lesions are predominant in advanced stages of CLL, particularly in patients without mutated *IGHV* genes. The most frequent chromosomal aberration, the 13q14 deletion, and a normal karyotype are associated with good prognosis. Trisomy 12 has