Preventing Latent Tuberculosis among HIV-Infected Patients: Efficacious and Effective, yet Inefficient?

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That preventive therapy works, if taken as prescribed, has been shown over and over again—or has it? In 1986, the data from the largest preventive therapy trial ever conducted, coordinated by The International Union Against Tuberculosis and Lung Disease in eastern Europe, under the authoritative analytic guidance of the US Centers for Disease Control and Prevention [1, 2], were reanalyzed [3]. In a comparison of 3, 6, and 12 months of isoniazid preventive chemotherapy with placebo, preventive chemotherapy of 6 months duration was found to be the most cost-effective choice. Voices arguing that efficacy, rather than effectiveness, should be the most important consideration seemingly went unheard when the official statement of the American Thoracic Society, co-signed by the Centers for Disease Control and Prevention, subsequently suggested that 6 months of preventive chemotherapy might be acceptable have been global: in virtually any international document concerned with the role of preventive therapy for the 2 billion or more persons with latent infection in the world, 6 months of isoniazid are recommended, without the precautionary provisos found in the US statements. Furthermore, none of the properly designed trials conducted among HIV-infected persons in sub-Saharan Africa used a regimen longer than 6 months. In 1 of these trials, there were more cases among patients who received preventive therapy than among placebo recipients, although the difference was statistically insignificant [6]. In another trial, any efficacy shown initially was lost within 1 year of follow-up [7]. What might, then, be expected in clinical practice?

In this issue of Clinical Infectious Diseases, a report from the Swiss HIV Cohort Study gives impressive testimony to the effectiveness of preventive therapy in routine clinical practice [8]. Not a single case of tuberculosis emerged during follow-up among the 144 HIV-infected persons who met the criteria for and received preventive therapy, whereas there were 16 cases among the 246 persons who met the criteria but were, for one reason or another, not given preventive therapy (table 1). The intervention was possibly also cost-effective: on average, only 15 persons had to be treated to prevent 1 case of tuberculosis, and as few as 8 persons had to be treated to prevent 1 case among persons from countries with a higher tuberculosis burden who had come under the care of the study clinics. Nevertheless, only 14% of all expected cases were actually prevented. This disappointing impact is largely due to the failure of clinicians to adhere to recommendations for tuberculosis skin testing and to provide preventive therapy if indicated. In part, it is also attributable to the emergence of patients classified as ineligible for preventive therapy because of a tuberculosis skin test induration <5 mm in diameter.

The amount of clinical work associated with the preventive efforts was considerable: >4000 tuberculin skin tests were performed, but the overall impact was disappointingly small. Clearly, preventive therapy is not as efficient an intervention as one would hope and has become even less efficient, because antiretroviral therapy has greatly reduced the incidence of tuberculosis among individuals with latent Mycobacterium tuberculosis infection.

To what extent would replacing the tuberculin skin test with an IFN-γ release assay (IGRA) improve the efficiency of the intervention? Some, but not much, is probably the short answer. There can be
Table 1. Incidence of tuberculosis in the Swiss HIV Cohort Study and use of preventive therapy.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>No. of patients</th>
<th>No. of observed cases</th>
<th>No. of averted cases</th>
<th>No. of expected cases</th>
<th>Averted cases, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not tested, no preventive therapy</td>
<td>1837</td>
<td>30</td>
<td>0</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Tested with negative results, no preventive therapy</td>
<td>3744</td>
<td>10</td>
<td>0</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Tested with positive results, no preventive therapy</td>
<td>246</td>
<td>16</td>
<td>0</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Not tested, preventive therapy given</td>
<td>13</td>
<td>0</td>
<td>0.2</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Tested with negative results, preventive therapy given</td>
<td>34</td>
<td>0</td>
<td>0.1</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Tested with positive results, preventive therapy given</td>
<td>144</td>
<td>0</td>
<td>9.4</td>
<td>9.4</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6018</td>
<td>56</td>
<td>9.7</td>
<td>65.7</td>
<td>14.7</td>
</tr>
</tbody>
</table>

little doubt about the superior specificity of IGRA, compared with the conventional tuberculin skin test [9]. Higher specificity will importantly reduce the number of persons treated unnecessarily. Therefore, it has a substantial impacts on effectiveness but has barely any impact on efficiency. Although the issue of comparative test sensitivity remains debatable [10], there is no reason to believe that the sensitivity of the IGRA deviates much from that of tuberculin skin testing. It is unlikely that any of the currently available IGRA has the potential to eliminate the fundamental issue of anergy, because this might be the biological limitation of this type of test. Again, probably little can be expected in terms of improving efficiency.

It is not within the ability of these newer tests to resolve a single fundamental problem associated with the tuberculin skin test, and that is the obvious prerequisite to place a test in the first place. Nor will these tests help in addressing the seeming reluctance of some clinicians to act on a positive test result, whatever the definition or test operating characteristics. The operational difficulties in the Swiss study are not specific to this particular European country; clinician adherence to testing HIV-infected persons is equally poor in the United States [11], where, historically, preventive therapy has perhaps the longest acceptance.

Therefore, we are confronted with a seemingly paradoxical situation, in that HIV infection is the strongest risk factor ever identified for progression of latent tuberculosis to active tuberculosis; we have modern tests available, with a largely improved specificity; we have an intervention that is efficacious and effective; and yet, incorporating all of these factors into our preventive efforts in daily clinical practice, we end up with a rather inefficient intervention. The underlying reasons for this failure in practice have nothing to do with better diagnostic tests or more-effective preventive therapy. Here, too, we are seemingly stuck with an intervention “in need of improvement” [12, p. 355] that still awaits a real breakthrough that can convince a larger proportion of clinical practitioners to adhere to guidelines issued by the professional associations.

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References