The Molecular Epidemiology of Tuberculosis in Settings With a High HIV Prevalence: Implications for Control

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(See the major article by Middelkoop et al on pages 53–61.)

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Tuberculosis control is extremely challenging in settings with a high prevalence of human immunodeficiency virus (HIV) infection. It was recognized years ago that the World Health Organization (WHO) directly observed therapy short-course (DOTS) strategy in isolation was insufficient to control tuberculosis in such settings [1]. Since then, various additional interventions have been considered, including the scale up of antiretroviral therapy (ART) [2, 3], enhanced tuberculosis case finding and household interventions [4], and isoniazid preventive therapy [5]. While the uptake of preventive therapy is challenging [6], the effectiveness of mass preventive therapy was disappointing [7], and the effectiveness of intensified case finding remains unproven [4, 8, 9], the scale up of ART appears promising [3, 10], particularly since the latest expansion of the WHO eligibility criteria for ART [11]. The long-term effect of ART on tuberculosis incidence may be less favorable, as the increasing life expectancy of HIV-infected individuals may increase their cumulative tuberculosis risk [12].

In this issue of the Journal, Middelkoop et al describe the molecular epidemiology of tuberculosis in a suburb of Cape Town, South Africa, with extremely high rates of tuberculosis and HIV infection [13]. Their study suggests that HIV-uninfected patients with tuberculosis contributed disproportionately to tuberculosis transmission in this setting and that cases of tuberculosis in HIV-infected patients were particularly likely to be secondary cases, even if the patients were receiving ART. A protective effect of ART against tuberculosis was not demonstrated in this study. It should be noted that the number of individuals receiving ART was small and that patients receiving ART may have had relatively low CD4+ T-cell counts, potentially resulting in bias against finding a protective effect of ART in this observational study. Finally, tuberculosis transmission within households was relatively uncommon among adults. While it had previously been shown that HIV-negative patients with tuberculosis contributed disproportionately to tuberculosis prevalence and, therefore, presumably to tuberculosis transmission among miners [14], Middelkoop et al suggest a disproportional impact of HIV-negative tuberculosis patients on transmission in the general population, using a molecular epidemiological approach.

What are the implications of these study findings for strategies and further studies to control tuberculosis in settings with a high HIV prevalence? First, given the limited uptake of ART in this setting, demonstration studies are needed to show the impact of the scale up of ART on tuberculosis transmission and incidence as the new WHO ART guidelines are being implemented. While initial results [3] and modeling studies [10, 12] are encouraging, monitoring tuberculosis incidence in patients with and those without HIV infection in relation to the roll out of ART is important to determine the extent to which the predicted impact is, indeed, achieved [15]. In the short term, ART is likely to reduce the incidence of tuberculosis among the HIV-infected individuals receiving ART [16], although this effect may be less pronounced over time as ART increases life expectancy and may, thus, increase the cumulative lifetime risk of tuberculosis [12]. However, over time ART may reduce the prevalence of HIV infection [17] and, thus, reduce the size of the population particularly susceptible to tuberculosis. Second, it is clear that HIV-focused interventions will not be sufficient. Protection of the HIV-infected population requires a reduction of their exposure to non-HIV-infected index cases. In settings such as in Cape Town, very limited benefit may be expected from interventions in the households of tuberculosis cases [13, 18]. While intensified case finding is theoretically appealing, it has yielded mixed results to date [4, 8, 9]. Further work is needed to...
identify successful approaches to detect and treat tuberculosis cases more quickly and, thus, reduce the infection pressure in vulnerable populations.

**Note**

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**References**