

Primary Transmission of Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis among HIV-Infected Persons: What Does the Future Hold in Store?

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(See the article by Andrews et al., on pages 1582–9.)

The article by Andrews et al. demonstrating exogenous reinfection as a cause of multidrug-resistant (MDR) and extensively drug resistant (XDR) tuberculosis (TB) in South Africa in the current issue of the *Journal* brings chilling news [1]. The authors report that all of the MDR and XDR TB that occurred in patients previously treated for TB was the result of primary transmission, rather than emerging as a result of inappropriate or inadequate treatment. All 17 of the subjects who they identified with MDR and/or XDR TB after an episode of drug-susceptible TB had been reinfected, and none of the cases were relapses with acquired drug resistance. This striking preponderance of reinfection suggests that exposure to and primary infection with MDR and/or XDR TB is the predominant mode of acquiring MDR and/or XDR TB in this population. This finding indicates that efforts to strengthen

existing TB treatment programs in this and similar settings by focusing on improving adherence to treatment of drug-susceptible TB will not stem the epidemic of MDR and XDR TB [2].

While it is, of course, important to optimize primary TB treatment by using directly observed treatment, short course, controlling the primary spread of MDR TB will require that all patients with recurrent TB undergo DNA-based rapid resistance testing to establish a diagnosis of MDR infection. Such tests are now available, and they can identify MDR TB within 24 h [3]. Rapid identification allows a potentially effective regimen to be instituted without a 4–6 week delay, and elimination of this delay can be life saving. In addition, patients' initial isolates should undergo primary susceptibility testing for second-line drugs, so that individually tailored "optimized" regimens can be instituted as soon as possible, as recommended by the World Health Organization [4]. The mortality of the patients in the Andrews et al. [1] report was very high—15 of 17—but reports in the literature suggest that prompt administration of adequate regimens can achieve better results than were observed by Andrews et al.; studies of the treatment of MDR TB in HIV-infected persons involved in outbreaks of MDR TB in New York in the 1990s dem-

onstrated clinical response rates to MDR TB treatment as low as 20% [5] and as high as 59% [6] and a median survival time as short as 66 days [5] and as long as 315 days [6] for these patients, even in the era before highly active antiretroviral therapy [5, 6]. Prompt administration of individualized regimens provides the best chance for cure and reduces the risk of further drug resistance emerging [5–7].

Because all the patients in the Andrews et al. [1] study had been hospitalized prior to the diagnosis of MDR and/or XDR TB, nosocomial spread could account for the high rate of primary MDR and/or XDR disease. However, the substantial variability of the isolates, both by molecular typing and antibiotic susceptibility testing, indicates that this is not a point-source outbreak, as has usually been the case in nosocomial MDR TB outbreaks [5, 8, 9]. Although it is possible that the reinfections observed by Andrews et al. [1] were acquired in multiple nosocomial exposures, the marked variability of the isolates suggests that most, if not all, were acquired in the community after discharge from the hospital. The fact that all patients had a history of previous hospitalization may only reflect the expected experience of the study population, namely, persons who had had a previous episode of TB.

The logical conclusion is that primary

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transmission is the predominant way that MDR and/or XDR TB is spread among persons in this community, not just among those with recurrent TB. If substantial community acquisition of MDR and/or XDR TB is occurring among HIV-infected persons, then improved hospital infection control, while essential, will not stem the tide of MDR and XDR TB. Rather, DNA-based resistance testing and primary susceptibility testing for second-line drugs will need to be undertaken for all new cases of TB. Only with such an aggressive approach can the clinical outcomes be improved for patients in this setting who have HIV infection and MDR and/or XDR TB.

A high proportion of reinfection with drug-susceptible tuberculosis has previously been reported among persons with advanced HIV infection [10, 11]. Such reinfection strongly suggests that HIV-infected persons, especially those with untreated advanced HIV disease, are not only at increased risk for TB disease if infected [12–14], but are also at increased risk for acquisition of infection if exposed. This increased susceptibility of HIV-infected persons to infection with *Mycobacterium tuberculosis* indicates that infection control measures to prevent acquisition of *M. tuberculosis* by such persons will need to be even more rigorous than infection control measures to prevent *M. tuberculosis* transmission to HIV-uninfected persons. In addition, casual exposures in the community may lead to acquisition of *M. tuberculosis* by HIV-infected persons, whereas these same exposures might not lead to acquisition of *M. tuberculosis* by HIV-uninfected persons. Therefore, contact investigations may need to expand their focus

past close contacts when casually exposed individuals have HIV infection, even if HIV-uninfected close contacts did not become infected. In addition, HIV-infected persons, especially those with advanced disease, need to be especially vigilant about avoiding potential exposure to persons with infectious TB. Given that the identification and avoidance of such exposures will be challenging, if not impossible, treatment of the underlying HIV disease with antiretroviral agents to restore immune protection and reduce the susceptibility to casual exposures may be the only practical prevention strategy.

This report identifies clear challenges to our ability to combat the epidemic of MDR and XDR TB in HIV-infected populations. We will need to make substantial improvements in infection control to prevent transmission of *M. tuberculosis* in hospitals and outpatient clinics, we will need to substantially increase the speed with which we identify and initiate treatment for MDR and XDR TB, and we will need to expand antiretroviral coverage for HIV-infected persons throughout the community. The magnitude and severity of the problem suggest that if we do not successfully implement all 3 of these strategies, we will see a continually expanding epidemic of MDR and XDR TB .

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