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A killer combination that must be stopped

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Multidrug-resistant tuberculosis (MDR-TB) is associated with poor treatment outcomes, but MDR-TB among HIV-infected persons might be substantially worse. While meta-analyses have been conducted of MDR-TB treatment outcomes globally,[1–3] none of these have separately analyzed outcomes among HIV/MDR-TB co-infected individuals.

In this issue of the *Journal*, Isaakidis and colleagues describe the results of a meta-analysis of studies of MDR-TB treatment outcomes among HIV co-infected adults and children.[4] The overall treatment success rate among HIV-infected adults—about 43% to 57%, depending on the studies included in the analysis—is similar to, or slightly worse than, the 54% to 62% rate for the MDR-TB infected population at large.[1–3] However, their findings also suggest that HIV/MDR-TB infected adults on treatment may have a substantially higher (29% to 38%) mortality rate,[4] as compared to 11% to 15% in the overall MDR-TB population.[1–3]

What makes HIV and MDR-TB such a killer combination? The causes are almost certainly multi-factorial, but delays in diagnosis and appropriate therapy for both diseases likely contribute to poor outcomes.

Late initiation of antiretroviral therapy (ART) may contribute to high mortality among HIV/MDR-TB co-infected individuals due to poor immune response against TB, and death from other opportunistic infections. Indeed, observational data suggest that early initiation of ART during MDR-TB treatment may improve outcomes,[5] similar to the findings of randomized trials for HIV-infected individuals with mostly drug-susceptible TB.[6] Unfortunately, despite increasing ART coverage in high HIV-burden countries in recent years, late initiation of ART (i.e. at very low CD4 counts) continues to be very common.[7]

Reducing mortality from MDR-TB in people living with HIV will also require aggressive and early diagnosis of MDR-TB using rapid tests such as Xpert MTB/RIF and line probe

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assays, followed by comprehensive drug-susceptibility testing (DST) using liquid cultures. In ART programs in resource-limited settings, availability and use of molecular and DST still lag substantially behind the use of sputum smear microscopy, which remains the initial (and often only) diagnostic test in many clinics.[8] Heavy reliance on smear microscopy is clearly inadequate in the face of HIV and MDR-TB. Countries with high prevalence of both infections must transition to better testing algorithms. South Africa has shown leadership in this area.

Lack of early DST may result in initial use of inappropriate treatment regimens, thereby increasing mortality. As in other studies, the analysis by Isaakidis et al. suggests that more aggressive treatment regimens (i.e., use fluoroquinolones, aminoglycosides, and Group IV drugs) were associated with better outcomes.[2,3] Prior meta-analyses have also suggested that individualized MDR-TB drug regimens may result in better outcomes than standardized regimens, again highlighting the central importance of DST-guided MDR-TB therapy.[1]

The high mortality rate in HIV/MDR-TB co-infected patients brings attention to systemic weaknesses in the management of both epidemics, and lack of integration of TB and HIV control activities on the ground. Addressing these systemic gaps is crucial for reducing mortality in this vulnerable population and for making progress towards the goals set out in the “Defeating AIDS”[9] and “End TB” strategies.[10]

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