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**Benzodiazepines, regardless of half-life, are associated with adverse respiratory outcomes across COPD severity** http://ow.ly/DgoFp

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# HIV and multidrug-resistant tuberculosis: overlapping risk factors

*To the Editor:*

Recent meta-analyses have indicated that, on average, new HIV-positive tuberculosis (TB) patients are at increased risk of multidrug-resistant (MDR)-TB compared with HIV-negative patients, while this risk is less clear for previously treated TB patients [1, 2]. In a recent issue of the *European Respiratory Journal*, Dean *et al.* [3] reported an association between HIV infection and MDR-TB disease based on aggregated data reported annually to the World Health Organization. Out of 24 countries where ⩾75% of TB patients had a HIV test result and at least one HIV-positive MDR-TB case was reported, 11 showed a significant positive association between HIV and multidrug resistance among TB patients, mostly in countries with a high prevalence of multidrug resistance. One of these countries was Kazakhstan, which added data for 40 975 out of the 104 781 patients included in their report.

The authors pointed out that there are likely to be risk factors common to HIV-positive and MDR-TB patients that could not be explored in their analysis. They refer to a study from Moldova, where detailed analysis of 2007–2010 surveillance data showed that the positive association observed among new patients remained after adjustment for potential confounders [4]. We would like to refer to a similar analysis

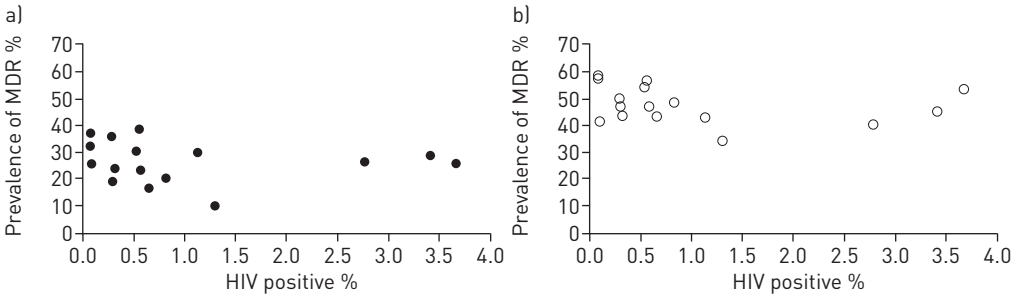


FIGURE 1 Prevalence of multidrug resistance (MDR) and HIV among a) new and b) previously treated tuberculosis patients in Kazakhstan, 2007–2011.

performed in Kazakhstan [5]. Using routine data from the electronic, national TB register from 2007–2011, we assessed patient characteristics associated with MDR-TB and/or HIV. In Kazakhstan, all patients are tested for HIV and TB drug resistance. HIV test results were available for 97% of TB patients and drug susceptibility test results for 93% of culture-positive patients. The proportion of TB patients with HIV increased from 0.6% in 2007 to 1.5% in 2011. The proportion of TB patients with multidrug resistance was high but did not change over time; on average, it was 36.1% for new and retreatment patients combined. In a crude analysis, among all 50 589 TB patients with HIV and drug susceptibility test results available, we observed a 20% higher prevalence of MDR-TB among HIV-positive patients than among HIV-negative patients (OR 1.2, 95% CI 1.02–1.4). Our results revealed that risk factors among TB patients for HIV and multidrug resistance were largely overlapping; in a univariate analysis, both included male sex, young adult age, urban residence, a history of incarceration, homelessness and drug abuse. Moreover, after adjustment for these overlapping risk factors in addition to demographics and treatment history, this association disappeared completely (adjusted OR 1.0, 95% CI 0.86–1.2). In addition, at the regional level, no clear association was observed between the prevalence of multidrug resistance and HIV (fig. 1). On average, 0.6% of the TB patients were infected both with HIV and MDR-TB *Mycobacterium tuberculosis*, but this risk varied greatly. TB patients at highest risk of being infected both with HIV and MDR-TB *M. tuberculosis* were those using drugs (12.5%) and those with a history of imprisonment (3.4%). These findings indicate that in Kazakhstan, the dual epidemic of HIV and MDR-TB is converging in specific socially vulnerable groups, and that enhanced efforts are necessary to provide (access to) diagnosis, TB/HIV treatment and care to these groups. This is important as both HIV and MDR-TB put patients at increased risk of treatment failure and mortality, and their combination is even more dangerous [6, 7]. Determinants of HIV and multidrug resistance are at least partly setting-specific and whether there is an independent association between them also may be situational. Therefore, it is important that more countries assess whether specific determinants may explain an apparent crude association between HIV and MDR-TB. This will require additional data collection beyond that available in routine surveillance registers in most settings.

@ERSpublications
**Overlapping risk factors may explain observed association between HIV and drug resistance in TB patients** http://ow.ly/DdRGT

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# The role of therapeutic drug monitoring in individualised drug dosage and exposure measurement in tuberculosis and HIV co-infection

*To the Editor:*

We read with interest the paper by Esposito *et al.* [1] reporting a difficult-to-treat extensively drug-resistant tuberculosis (TB) case. TB treatment in HIV-positive individuals can also be particularly challenging. An HIV-positive 26-year-old male showing excessive weight loss (body mass index 17.5 $kg \cdot m^{-2}$) and clinical deterioration was admitted to the Beatrixoord Tuberculosis Centre (University Medical Center Groningen, Haren, the Netherlands) for the treatment of pulmonary TB. *Mycobacterium tuberculosis* isolated from sputum appeared susceptible to all first-line drugs tested. The patient received rifampicin (RIF) (600 mg), isoniazid (300 mg), pyrazinamide (1500 mg) and ethambutol (1200 mg) under directly observed therapy. He started with emtricitabine (200 mg), tenofovir (245 mg) and raltegravir (800 mg twice daily) 2 weeks later as combination antiretroviral therapy. Therapeutic drug monitoring (TDM) was performed to evaluate the extent of the effect of RIF on raltegravir. Multiple blood samples were drawn over a period of 12 h to evaluate RIF exposure. Although raltegravir concentrations were adequate, strikingly low RIF concentrations were measured [2]. Unfortunately, RIF concentrations were not measured in an earlier stage of the treatment. Newly obtained plasma samples confirmed the low RIF concentration. To detect a potential decreased absorption, the same dosage of RIF was administered intravenously, which resulted in an acceptable RIF exposure (fig. 1). Drug–drug interactions influencing the absorption of RIF were not expected based on the concomitantly administered medication. The patient had no gastro-intestinal complaints and the faeces showed no presence of *Giardia lamblia*, *Entamoeba histolytica* and *Cryptosporidium* spp. Between the start of the TB treatment and the TDM day he had gained 11.2 kg. No obvious signs were present that could account for the remarkably low drug exposure after oral administration. However, despite the decreased bioavailability of RIF, the patient responded well to therapy. Because a decreased bioavailability was noticed in a late phase of treatment and considering the positive treatment outcome, it was decided not to change treatment. The patient has remained clinically well and free of relapse 2 years after completion of TB treatment.

Drug exposure of first-line anti-TB drugs has gained renewed interest after the hollow-fibre infection model showed that the effectiveness of these drugs is driven by the ratio of area under the curve (AUC) of concentration–time to minimum inhibitory concentration (MIC) [3]. In addition, evidence is accumulating that subtherapeutic concentrations may contribute to acquired drug resistance and treatment failure [4]. A reduction of anti-TB drug exposure, in particular RIF, in HIV patients was reported earlier [5], but not in all studies [6]. Enteropathy caused by parasitic infections or by HIV itself (enterocyte apoptosis) and diarrhoea can often explain the reduced drug absorption in HIV patients. In our patient, the AUC from time zero to 24 h after dosing ($AUC_{0–24}$) was 2.43 $mg \cdot h \cdot L^{-1}$ after oral administration and 29.92 $mg \cdot h \cdot L^{-1}$ after *i.v.* administration, resulting in an estimated bioavailability of 8.12%. For this specific case we speculate that the exposures of concomitantly administered anti-TB drugs were sufficient and