



# Is Multi-Drug Resistant Tuberculosis More Prevalent in HIV-Infected Patients in Korea?

Shinwon Lee<sup>1</sup>, Sun Hee Lee<sup>1</sup>, Jeong Ha Mok<sup>1</sup>, Su Jin Lee<sup>2</sup>, Kye-Hyung Kim<sup>1</sup>,  
Jeong Eun Lee<sup>1</sup>, Seung Geun Lee<sup>1</sup>, Joo Seop Chung<sup>1</sup>, and Ihm Soo Kwak<sup>1</sup>

<sup>1</sup>Department of Internal Medicine, Pusan National University School of Medicine, Medical Research Institute, Pusan National University Hospital, Busan;

<sup>2</sup>Department of Internal Medicine, Pusan National University School of Medicine, Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan, Korea.

The epidemiological synergy between human immunodeficiency virus (HIV) and tuberculosis (TB) is a major threat to public health. However, the association between HIV and multi-drug resistant tuberculosis (MDR-TB) is not clear. To explore the association between HIV and MDR-TB infection, a case-control study was performed in Korea. A total of 1606 culture-proven TB patients (45 HIV vs. 1561 non-HIV) from January 2006 to October 2014 were included in this analysis. MDR-TB rates were 11.1% and 8.2% in the HIV and non-HIV groups, respectively ( $p=0.42$ ), thus indicating that MDR-TB was not significantly associated with HIV infection in Korea.

**Key Words:** MDR, HIV, resistance, intermediate TB burden

Multi-drug resistant tuberculosis (MDR-TB) is a widespread public health problem and major challenge for tuberculosis (TB) control programs.<sup>1</sup> The prevalence of human immunodeficiency virus (HIV) is strongly correlated with an increased incidence of TB, and co-infection with HIV presents another challenge in TB control.<sup>1,2</sup> Co-infection with HIV can accelerate the progression of TB prior to anti-TB medication, thus MDR-TB can be a higher risk factor for death in HIV-infected patients.<sup>3,4</sup>

The relationship between the two infections is not yet clearly understood.<sup>5</sup> Previous studies on the association between HIV infection and MDR-TB from different settings and countries have been discordant.<sup>5,6</sup> These findings suggest that epidemiological factors such as the burden of HIV or TB infection in a cer-

tain area are important aspects that affect the association between HIV and MDR-TB infection.

Most previous studies have been conducted in areas with high HIV prevalence and low MDR-TB prevalence, whereas some studies have been conducted in low HIV prevalent areas. Nevertheless, most were conducted in situations with institutional outbreaks.<sup>6</sup> It is important to know the MDR-TB rate in HIV/TB co-infected patients, because TB progresses more rapidly in HIV patients, and the turn-around time of the drug susceptibility test is very long. There are few studies that have adequately addressed the MDR-TB burden of HIV-infected patients in an area with low HIV prevalence and intermediate TB burden. In South Korea, the prevalence of HIV and TB is low and intermediate (incidence rate of TB: 86/100000 population), respectively,<sup>1,7</sup> therefore, evaluated the association between HIV and MDR-TB infection in an area with low HIV prevalence and intermediate TB burden.

To determine the association between HIV and MDR-TB infection, a retrospective case-control study was performed. All culture positive and susceptibility reported TB patients aged 18 years and older who visited Pusan National University Hospital from January 2006 to October 2014 were enrolled.

The drug resistance rate, MDR, and extensively drug resistant tuberculosis (XDR-TB) rates were compared between the

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**Corresponding author:** Dr. Sun Hee Lee, Department of Internal Medicine, Pusan National University Hospital, 179 Gudeok-ro, Seo-gu, Busan 49241, Korea.  
Tel: 82-51-240-7673, Fax: 82-51-247-3213, E-mail: zzanmery@gmail.com

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HIV-infected and non-HIV-infected groups. MDR-TB was defined as *in vitro* resistance to at least both isoniazid (INH) and rifampin (RIF).<sup>8</sup> XDR-TB was defined as resistance to any fluoroquinolone and at least one of three second-line injectable drugs (capreomycin, kanamycin, and amikacin) in addition to multidrug resistance.<sup>8</sup> New patients were defined as those who had taken anti-TB drugs for less than 1 month or never been treated for TB. Finally, previously treated patients were defined as those who received 1 month or more of anti-TB drugs in the past.<sup>9</sup>

Between January 2006 to October 2014, all patients whose culture test was positive for *Mycobacterium tuberculosis* and accompanied by an antimicrobial susceptibility report were identified from a microbiology database. Demographic data, history of previous TB treatment, antimicrobial susceptibility, and clinical data were retrospectively reviewed. The Institutional Review Board at Pusan National University Hospital approved the study protocol (No. E-201 5142).

Data were analyzed using SPSS software, version 18.0 (SPSS Inc. and IBM Company, Chicago, IL, USA). Fisher's exact test or Pearson  $\chi^2$  test was used to compare categorical variables, and continuous variables were compared using Student's t-test. All tests of significance were two-tailed;  $p \leq 0.05$  was considered to be statistically significant.

Among 1796 culture-positive and susceptibility reported TB patients, 1606 patients whose previous treatment history of TB was available were included in this analysis. A total of 95.5% of *Mycobacterium tuberculosis* cultures were performed on pulmonary specimens such as sputum or bronchial aspirates, and 4.5% were performed on extrapulmonary specimens such as tissues or body fluid of various sites. The mean age of included patients was  $53.2 \pm 18.3$  years, and 59.4% were male. One hundred and thirty-three patients (8.8%) had MDR-TB, and the

overall mortality of MDR-TB was higher than non-MDR-TB. Previous treatment history of TB was significantly associated with MDR-TB [odds ratio (OR) 3.79, 95% confidence interval (CI) 2.60–5.52,  $p < 0.01$ ]. Forty-five patients were co-infected with HIV, and 1561 were not. Disseminated TB (HIV group 37.8% vs. non-HIV group 2.0%,  $p < 0.01$ ) and central nervous system involvement (HIV group 11.1% vs. non-HIV group 0.7%,  $p < 0.01$ ) were more prevalent in the HIV group. In the HIV group, 11.1, 13.3, 0, and 6.7% were resistant to RIF, INH, ofloxacin, and aminoglycoside, respectively. The resistance rates were not significantly higher in HIV infected patients. MDR and XDR-TB were 11.1% (5/45) and 0% (0/45) in the HIV group and 8.2% (128/1561) and 1.8% (28/1561) in the non-HIV group, respectively: MDR and XDR-TB were not significantly associated with HIV infection (HIV group vs. non-HIV group, OR 1.40, 95% CI 0.54–3.61,  $p = 0.42$ ). In a subgroup analysis of new patients, MDR-TB was not significantly higher in the HIV group (HIV group vs. non-HIV group OR 1.82, 95% CI 0.63–5.25,  $p = 0.29$ ) (Table 1).

Our study demonstrated that the rate of MDR-TB in south-east Korea was 11.1%, and it was not significantly associated with HIV infection. In addition, MDR-TB was not associated with HIV infection in a subgroup analysis of new TB patients. Joh, et al.<sup>10</sup> reported that the MDR-TB prevalence among HIV/TB co-infected patients was 32.7% at a Korean hospital. However, they did not compare MDR-TB rate of HIV-infected patients with the control group.<sup>10</sup> Therefore, based on the previous study, it is not clear whether MDR-TB rate is more frequent in HIV-infected patients. Furthermore, the previous study was performed at a referral hospital for complicated HIV/AIDS patients,<sup>10</sup> therefore, those patients could have been selectively gathered at that institution. Our study suggests that the MDR-TB burden of HIV-infected patients might be similar to the

**Table 1.** Comparison of Antimicrobial Resistance and Rate of MDR-TB between HIV and Non-HIV Infected Patients

	HIV group	Non-HIV group	Odds ratio (95% CI)	p value
Total (HIV, n=45 vs. non HIV, n=1561)				
MDR-TB	5 (11.1%)	128 (8.2%)	1.40 (0.54–3.61)	0.42
INH resistance	6 (13.3%)	254 (16.3%)	0.79 (0.33–1.89)	0.60
RFP resistance	5 (11.1%)	136 (8.7%)	1.31 (0.51–3.37)	0.60
PZA resistance	2 (4.4%)	75 (4.8%)	0.92 (0.22–3.88)	>0.99
New cases (HIV, n=40 vs. non HIV, n=1322)				
MDR-TB	4 (10%)	76 (5.7%)	1.82 (0.63–5.25)	0.29
INH resistance	4 (10%)	175 (13.2%)	0.73 (0.26–2.07)	0.55
RFP resistance	4 (10%)	82 (6.2%)	1.68 (0.58–4.84)	0.31
PZA resistance	2 (5%)	44 (3.3%)	1.43 (0.36–6.54)	0.40
Pulmonary TB (HIV, n=22 vs. non HIV, n=1425)				
MDR-TB	3 (13.6%)	121 (8.5%)	1.70 (0.50–5.83)	0.43
INH resistance	4 (18.2%)	240 (16.8%)	1.10 (0.37–3.27)	0.78
RFP resistance	3 (13.6%)	128 (9%)	1.60 (0.47–5.48)	0.44
PZA resistance	2 (9.1%)	71 (5%)	1.91 (0.44–8.32)	0.31

MDR, multi-drug resistance; TB, tuberculosis; INH, isoniazid; RFP, rifampin; PZA, pyrazinamide; HIV, human immunodeficiency virus.

MDR-TB burden of the general population in areas with low HIV and intermediate TB burden such as South Korea, Japan, Malaysia, Singapore, and Hong Kong.

Busan has the highest incidence of HIV infection and TB in Korea; indeed, our institute has the largest HIV and TB care centers in southeast Korea. A total of 844 HIV-infected patients (about 70% of HIV patients who were notified) in southeast Korea received care at our institute during the study period. This is the first case-control study that compared the MDR-TB rate in HIV-infected patients to that of a control group. Therefore, our finding provides useful epidemiological information regarding MDR-TB/HIV co-infection in southeast Korea. Our findings could be applied also to all of Korea, although care must be taken when generalizing the finding, because it is a single center study.

MDR-TB was not uncommon among HIV-infected patients in our present study, although the rate was not significantly higher than in the general population. The patients with MDR-TB are more likely to receive inappropriate initial anti-TB treatment. Since progression of TB is rapid and fatal, MDR-TB may cause far more devastating consequences in HIV-infected patients. Previous studies have demonstrated that MDR-TB has a worse prognosis in HIV-infected patients than in the general population.<sup>6</sup> Rapid diagnosis of MDR-TB using a new molecular test can reduce time to initiation of MDR-TB treatment, culture conversion, and poor clinical outcomes, and can improve infection control practices.<sup>11</sup> The impact of a rapid MDR-TB diagnostic test can be greater in HIV/TB co-infected patients. Therefore, we suggest that all HIV-infected patients in South Korea who are suspected of having co-infection with TB should undergo MDR-TB diagnostic testing as early as possible.

In summary, HIV was not significantly associated with MDR-TB in southeast Korea, an area of low HIV prevalence and intermediate TB burden. However, MDR-TB was not uncommon in HIV infected patients in Korea. We, therefore, recommend that all HIV-infected patients in South Korea who are suspected of having co-infection with TB should undergo early MDR-TB diagnostic testing.

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