Infect Chemother. 2021 Dec;53(4):792-795
https://doi.org/10.3947/ic.2021.0085
pISSN 2093-2340·eISSN 2092-6448

Infection & Chemotherapy

Brief Communication

Prevalence of Multidrug-Resistant Tuberculosis in HIV/Tuberculosis Co-Infected Patients

Chan Mi Lee [1], **Eunyoung Lee** [2,3], **Ji Hwan Bang** [2,3], **Sang-Won Park** [2,3], **Wan Beom Park** [1,2], **Myoung-don Oh** [1,2], **and Nam Joong Kim** [1,2]

[1]Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea
[2]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea
[3]Department of Internal Medicine, Boramae Medical Center, Seoul, Korea

Received: Aug 11, 2021
Accepted: Nov 30, 2021

Corresponding Author:
Nam Joong Kim, MD, PhD
Department of Internal Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea.
Tel: +82-2-2072-2228
Fax: +82-2-762-9662
E-mail: molder@unitel.co.kr

ORCID iDs
Chan Mi Lee
https://orcid.org/0000-0001-7907-0412
Eunyoung Lee
https://orcid.org/0000-0001-8280-3605
Ji Hwan Bang
https://orcid.org/0000-0002-7628-1182
Sang-Won Park
https://orcid.org/0000-0002-0550-1897
Wan Beom Park
https://orcid.org/0000-0003-0022-9625
Myoung-don Oh
https://orcid.org/0000-0002-2344-7695
Nam Joong Kim
https://orcid.org/0000-0001-6793-9467

ABSTRACT

Tuberculosis (TB) is a common opportunistic infection in human immunodeficiency virus (HIV)-infected patients. Patients with multidrug-resistant (MDR)-TB have poor outcomes. This study aimed to determine the prevalence of MDR-TB in HIV/TB co-infected patients in the Korea. We reviewed the medical records of HIV/TB co-infected patients at two university hospitals between January 1998 and December 2020. During the study period, a total of 87 HIV/TB co-infected patients were identified, and drug susceptibility test results were available for 44 of them. The prevalence of MDR-TB in the study population was 15.9% (7/44, 95% confidence interval, 5.1 - 26.7).

Keywords: HIV; Tuberculosis; Tuberculosis, Multidrug-Resistant; Prevalence

Tuberculosis (TB) is the most common opportunistic infection in human immunodeficiency virus (HIV)-infected patients in the Korea [1, 2]. However, the incidence of HIV/TB co-infection has decreased after the introduction of antiretroviral therapy. The incidence of TB in HIV-infected patients was 9.6 cases/100 person-year (PY) [95% confidence interval (CI), 6.0 - 14.5 cases per 100 PY] between 1988 and 1997 and 1.19 cases/100 PY (95% CI, 0.91 - 1.47 cases per 100 PY) between 1998 and 2010 [3]. Among HIV-infected patients, those with multidrug-resistant (MDR)-TB are more likely to die and less likely to be cured or undergo complete treatment compared to those with non-MDR-TB [4]. The prevalence of MDR-TB varied from 11.1% to 32.7% in HIV/TB co-infected patients in the Korea [5, 6]. However, limited data are available on MDR-TB in HIV/TB co-infected patients, with the estimated prevalence of MDR-TB in this patient population varying considerably across studies. The present study aimed to investigate the prevalence of MDR-TB in HIV/TB co-infected patients in the Korea.

This descriptive retrospective study was conducted at the Seoul National University Hospital and Boramae Medical Center. The medical records of HIV/TB co-infected patients between January 1998 and December 2020 were reviewed. Only patients with culture-proven TB and available drug susceptibility test (DST) results were included. We used the World Health Organization definitions of MDR-TB and extensively drug-resistant (XDR)-TB [7]. MDR-TB was defined as resistance to both rifampin and isoniazid. XDR-TB was defined as MDR-TB

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Funding
None.

Conflict of Interest
NJK is editorial board of Infect Chemother; however, he did not involve in the peer reviewer selection, evaluation, and decision process of this article. WBP is associate editor of Infect Chemother; however, he did not involve in the peer reviewer selection, evaluation, and decision process of this article.

Author Contributions
Conceptualization: CML, NJK. Data curation: CML, EL, JHB. Investigation: SWP, WBP. Supervision: MDO, Writing-original draft: CML, NJK. Writing-review&editing: EL, JHB, SWP, WBP, MDO

along with resistance to any fluoroquinolone and at least one of three injectable second-line drugs (amikacin, kanamycin or capreomycin). DSTs were performed via the absolute concentration method using Lowenstein–Jensen agar medium prepared by the Korean Institute of Tuberculosis. Demographic data including age, sex, history of previous TB, and the presence of other acquired immunodeficiency syndrome (AIDS)-defining clinical illnesses were collected. Clinical data including TB lesion (pulmonary TB, extrapulmonary TB, and pulmonary plus extrapulmonary TB), CD4 cell count, and HIV viral load at the time of HIV diagnosis were collected. Moreover, data on CD4 cell count and HIV viral load at the time of HIV/TB co-infection diagnosis were collected and were defined as data collected within 4 weeks of TB diagnosis. Student *t*-test or Mann–Whitney *U* test was used to compare quantitative variables, and chi-square test or Fisher's exact test was used to compare categorical variables. *P*-values <0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS for Windows (version 26.0; SPSS Inc., Chicago, IL, USA). The study was approved by the Seoul National University Hospital Institutional Review Board (No. H-2103-204-1208).

In total, 87 HIV/TB co-infected patients were identified between January 1998 and December 2020. Of these 87 patients diagnosed with culture-proven TB, DST results were available for 44 patients. The prevalence of resistance to isoniazid and rifampin was 20.5% (9/44, 95% CI, 8.5 - 32.4) and 15.9% (7/44, 95% CI, 5.1 - 26.7), respectively, and that of MDR-TB and XDR-TB was 15.9% (7/44, 95% CI, 5.1 - 26.7) and 0% (0/44, 95% CI, 0.0 - 0.0), respectively. All cases of rifampin-resistant TB and 7 cases of isoniazid-resistant TB were MDR-TB, and 2 cases of isoniazid-resistant TB were isoniazid-monoresistant TB.

The demographic and clinical characteristics of the MDR-TB and non-MDR-TB groups are listed in **Table 1**. The mean age of the 44 patients was 46.9 ± 12.8 years, and 41 (93.2%) of them were

Table 1. Demographic and clinical characteristics of HIV/tuberculosis co-infected patients

Variables	Total (n = 44)	MDR-TB (n = 7)	Non-MDR-TB (n = 37)	*P*-value
Age, mean (± SD)	46.9 (± 12.8)	45.0 (± 10.1)	47.2 (± 13.3)	0.675
Male (%)	41 (93.2)	5 (71.4)	36 (97.3)	0.061
BMI, mean (± SD)	20.9 (± 4.66)	23.4 (± 2.54)	20.5 (± 4.81)	0.195
Transmission route				
Homosexual	14 (31.8)	3 (42.9)	11 (29.7)	0.092
Heterosexual	7 (15.9)	3 (42.9)	4 (10.8)	
Transfusion	0 (0)	0 (0)	0 (0)	
Unknown	22 (50.0)	1 (14.3)	21 (56.8)	
Others	1 (2.3)	0 (0)	1 (2.7)	
Initial CD4 cell count (cells/mm^3), median (IQR)	73 (29 - 298)	38 (26 - 380)	74 (29 - 295)	0.749
Initial HIV viral load (×10^3 copies/mL), median (IQR)	140 (36 - 310)	142 (17 - 202)	139 (36 - 482)	0.332
CD4 cell counts at TB diagnosis (cells/mm^3), median (IQR)	74 (28 - 176)	38 (26 - 200)	74 (30 - 176)	0.715
HIV viral load at TB diagnosis (×10^3 copies/mL), median (IQR)	78 (0 - 190)	105 (1 - 192)	69 (0 - 203)	0.437
Anti-retroviral therapy history				
Naïve	23 (52.3)	3 (42.9)	20 (54.1)	0.639
Ex, not ongoing	2 (4.5)	0 (0)	2 (5.4)	
Current	19 (43.2)	4 (57.1)	15 (40.5)	
TB lesion				
Pulmonary	16 (36.4)	3 (42.9)	13 (35.1)	0.329
Extrapulmonary	6 (13.6)	2 (28.6)	4 (10.8)	
Pulmonary + extrapulmonary	22 (50.0)	2 (29.6)	20 (54.1)	
Other AIDS-defining diseases	10 (22.7)	1 (14.3)	9 (24.3)	1.000
In-hospital mortality	2 (4.5)	1 (14.3)	1 (2.7)	0.296

HIV, human immunodeficiency virus; MDR-TB, multidrug resistant-tuberculosis; SD, standard deviation; BMI, body mass index; IQR, interquartile range; AIDS, acquired immunodeficiency syndrome.

https://doi.org/10.3947/ic.2021.0085

Table 2. Demographic and clinical characteristics of HIV/MDR-TB co-infected patients

Cases	Sex / Age	BMI	Transmission route	Initial CD4 cell count (cells/mm^3)	Initial viral load (×10^3 copies/mL)	CD4 cell count at TB diagnosis (cells/mm^3)	Viral load at TB diagnosis (×10^3 copies/mL)	Anti-retroviral therapy history	TB lesion	Other AIDS-defining diseases
Case 1	Male/45	-	Heterosexual	30	191,914	30	191,914	Current	Extrapulmonary	No
Case 2	Female/42	-	Heterosexual	200	141,906	200	156,000	Naïve	Pulmonary + Extrapulmonary	No
Case 3	Female/66	22.65	Heterosexual	380	202,000	99	1,370	Current	Pulmonary + Extrapulmonary	No
Case 4	Male/45	22.68	Homosexual	19	105,000	19	105,000	Naïve	Pulmonary	No
Case 5	Male/39	22.26	Homosexual	38	236,886	38	236,886	Naïve	Extrapulmonary	No
Case 6	Male/44	21.66	Unknown	720	5,949	1,000	0	Current	Pulmonary	No
Case 7	Male/34	27.91	Homosexual	26	16,647	26	16,647	Current	Pulmonary	Yes

HIV, human immunodeficiency virus; MDR-TB, multidrug resistant-tuberculosis; BMI, body mass index; AIDS, acquired immunodeficiency syndrome.

male. The proportion of pulmonary, extrapulmonary, and pulmonary plus extrapulmonary TB was 36.4% (16/44), 13.6% (6/44), and 50.0% (22/44), respectively. The median CD4 cell count and median HIV viral load within 4 weeks of TB diagnosis were 74 (28 - 176) cells/mm^3 and 78 (0 - 190) × 10^3 copies/mL, respectively. Homosexual transmission route was 42.9% (3/7) in the MDR-TB group and 29.7% (11/37) in the non-MDR-TB group. In-hospital mortality was 14.3% (1/7) in the MDR-TB group and 2.7% (1/37) in the non-MDR-TB group. The clinical characteristics of HIV/MDR-TB co-infected patients are described in **Table 2**.

Few studies have investigated the prevalence of MDR-TB in HIV/TB co-infected patients in the Korea. The present study results show that this prevalence was 15.9% (7/44) during the study period. The prevalence was not significantly changed during the study period (18.2% during 1998 - 2009, 13.6% during 2010 - 2020). In 2019, the prevalence of MDR-TB among patients with newly diagnosed TB was 2.4% in the Korea. Furthermore, the prevalence of MDR-TB in HIV/TB co-infected patients is higher than that in the general population in the Korea (approximately 3 - 6%) [8, 9]. Studies have reported varying results regarding the prevalence of MDR-TB among HIV/TB co-infected cases [5, 6]. One study reported that this prevalence was 32.7% (18/55) and that the median CD4 cell count at TB diagnosis was lower in the MDR-TB group than in the non-MDR-TB group (57 cells/mm^3 *vs.* 121 cells/mm^3) [6]. Another study reported that the prevalence of MDR-TB in the HIV group (11.1% [5/45]) and was not significantly different from that in the non-HIV group (8.2% [128/1,561]) [5]. Because the second study did not report the CD4 cell count, a clear comparison of the patient characteristics between the above two studies is not possible. Although a direct comparison of these results would be difficult, we presumed that the difference in the reported prevalence of MDR-TB between these two studies might be due to the difference in the study population. The median CD4 cell count at TB diagnosis in the present study population was lower than that reported in a previous study (74 cells/mm^3 *vs.* 90 cells/mm^3). Although AIDS-defining illnesses were reported to be more frequent in the MDR-TB group than in the non-MDR-TB group in a previous study, we did not observe any significant between-group difference regarding this in our study. Moreover, there was no significant between-group difference regarding CD4 cell count. The risk of treatment failure is higher in patients with MDR-TB than in those with non-MDR-TB, and this effect is more prominent in HIV-infected patients [10, 11]. Prompt initiation of appropriate anti-TB drugs is essential for treating HIV/TB co-infection. Therefore, DSTs must be performed to identify MDR-TB in HIV-infected patients with positive culture results for *Mycobacterium tuberculosis*. In the present study population, DST was performed in only 50.6% (44/87) of HIV/TB co-infected patients. Thus, further efforts are required to conduct DSTs in HIV/TB co-infected patients for initiating appropriate anti-TB drugs.

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This study has several limitations. First, DST results for *M. tuberculosis* were available for only 50.6% (44/87) of the investigated patients. Second, only seven patients were identified as having MDR-TB, and it is difficult to determine the risk factors for MDR-TB in HIV/TB co-infected patients. Further studies with a larger prospective cohort are needed to determine these risk factors.

In conclusion, we showed that the prevalence of MDR-TB in the HIV/TB co-infected patients was 15.9%, which is higher than that in the general population in the Korea. Considering the poor outcome of MDR-TB in HIV-infected patients, we recommend that DSTs should be performed early in HIV/TB co-infected patients to promptly initiate appropriate anti-TB drugs.

REFERENCES

1. Oh MD, Park SW, Kim HB, Kim US, Kim NJ, Choi HJ, Shin DH, Lee JS, Choe K. Spectrum of opportunistic infections and malignancies in patients with human immunodeficiency virus infection in South Korea. Clin Infect Dis 1999;29:1524-8.
PUBMED | CROSSREF
2. Choi Y, Choi BY, Kim SM, Kim SI, Kim J, Choi JY, Kim SW, Song JY, Kim YJ, Park DW, Kim HY, Choi HJ, Kee MK, Shin YH, Yoo M. Epidemiological characteristics of HIV infected Korean: Korea HIV/AIDS Cohort Study. Epidemiol Health 2019;41:e2019037.
PUBMED | CROSSREF
3. Hwang JH, Choe PG, Kim NH, Bang JH, Song KH, Park WB, Kim ES, Park SW, Kim HB, Kim NJ, Oh MD, Choe KW. Incidence and risk factors of tuberculosis in patients with human immunodeficiency virus infection. J Korean Med Sci 2013;28:374-7.
PUBMED | CROSSREF
4. Post FA, Grint D, Werlinrud AM, Panteleev A, Riekstina V, Malashenkov EA, Skrahina A, Duiculescu D, Podlekareva D, Karpov I, Bondarenko V, Chentsova N, Lundgren J, Mocroft A, Kirk O, Miro JM; HIV-TB Study Group. Multi-drug-resistant tuberculosis in HIV positive patients in Eastern Europe. J Infect 2014;68:259-63.
PUBMED | CROSSREF
5. Lee S, Lee SH, Mok JH, Lee SJ, Kim KH, Lee JE, Lee SG, Chung JS, Kwak IS. Is multi-drug resistant tuberculosis more prevalent in HIV-infected patients in Korea? Yonsei Med J 2016;57:1508-10.
PUBMED | CROSSREF
6. Joh JS, Hong HC, Jeong IA, Chin BS, Yang HJ, Choi H, Bang JH. Proportion of multidrug-resistant tuberculosis in human immunodeficiency virus/mycobacterium tuberculosis co-infected patients in Korea. J Korean Med Sci 2012;27:1143-6.
PUBMED | CROSSREF
7. World Health Organization (WHO). Meeting report of the WHO expert consultation on the definition of extensively drug resistant tuberculosis. Geneva: WHO; 2021.
8. Lee M, Han J, Kim YR, Kwak N, Kim JH, Park O, Shin S, Moon HS, Kim HJ, Jang MJ, Yim JJ. Multidrug-resistant tuberculosis in South Korea: a retrospective analysis of national registry data in 2011-2015. Int J Tuberc Lung Dis 2019;23:850-7.
PUBMED | CROSSREF
9. Kim H, Mok JH, Kang B, Lee T, Lee HK, Jang HJ, Cho YJ, Jeon D. Trend of multidrug and fluoroquinolone resistance in Mycobacterium tuberculosis isolates from 2010 to 2014 in Korea: a multicenter study. Korean J Intern Med 2019;34:344-52.
PUBMED | CROSSREF
10. Jeon DS, Shin DO, Park SK, Seo JE, Seo HS, Cho YS, Lee JY, Kim DY, Kong SJ, Kim YS, Shim TS. Treatment outcome and mortality among patients with multidrug-resistant tuberculosis in tuberculosis hospitals of the public sector. J Korean Med Sci 2011;26:33-41.
PUBMED | CROSSREF
11. Bhering M, Duarte R, Kritski A. Treatment outcomes and predictive factors for multidrug-resistant TB and HIV coinfection in Rio de Janeiro State, Brazil. Int J Tuberc Lung Dis 2021;25:292-8.
PUBMED | CROSSREF