MAJOR ARTICLE

Impact of Extensive Drug Resistance on Treatment Outcomes in Non–HIV-Infected Patients with Multidrug-Resistant Tuberculosis

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Background. Recently, serious concerns about extensively drug-resistant tuberculosis (XDR-TB), which shows resistance to second-line anti-TB drugs in addition to isoniazid and rifampicin, have been raised. The aim of this study was to elucidate the impact of extensive drug resistance on treatment outcomes in non–human immunodeficiency virus (HIV)–infected patients with multidrug-resistant tuberculosis (MDR-TB).

Methods. Patients who received the diagnosis of and treatment as having MDR-TB at Seoul National University Hospital (Seoul, Republic of Korea) between January 1996 and December 2005 were included. The definition of XDR-TB was TB caused by bacilli showing resistance to both isoniazid and rifampicin and also showing resistance to any fluoroquinolone and to at least 1 of the following 3 injectable anti-TB drugs: capreomycin, kanamycin, and amikacin. To identify the impact of extensive drug resistance on treatment outcomes, univariate comparison and multiple logistic regression were performed.

Results. A total of 211 non–HIV–infected patients with MDR-TB were included in the final analysis. Among them, 43 patients (20.4%) had XDR-TB. Treatment failure was observed in 19 patients (44.2%) with XDR-TB, whereas treatment of 46 patients (27.4%) with non–XDR-TB failed ($P = .057$). The presence of extensive drug resistance (adjusted odds ratio [OR], 4.46; 95% confidence interval [CI], 1.35–14.74) and underlying comorbidity (adjusted OR, 2.62; 95% CI, 1.00–6.87) were independent risk factors for treatment failure. However, a higher level of albumin was inversely associated with treatment failure (adjusted OR, 0.87; 95% CI, 0.77–0.97).

Conclusion. The presence of extensive drug resistance, the presence of comorbidity, and hypoalbuminemia were independent poor prognostic factors in non–HIV-infected patients with MDR-TB.

Multidrug-resistant tuberculosis (MDR-TB), resistant to at least both isoniazid and rifampicin, poses a serious threat to global health because it requires treatment for a long duration, frequent hospitalization, and subsequent higher cost of treatment, and it results in a considerable number of mortalities [1, 2]. According to a World Health Organization (WHO) report from 2000, 3.2% of all new TB cases are MDR. It is especially worrisome in Estonia and Latvia, where multidrug resistance was observed in 14% and 9% of new TB cases, respectively [3]. The treatment of MDR-TB is difficult because second-line drugs must be used, which are less potent than first-line drugs and are not as well tolerated. Early publications about the treatment response of MDR-TB reported considerable mortality, as high as 37% [4].

Concerns about extensively drug-resistant tuberculosis (XDR-TB), showing extensive resistance to second-line anti-TB drugs in addition to resistance to isoniazid and rifampicin, have recently been raised [5–8]. According to the recent survey, including 25 reference laboratories on 6 continents, 10% of MDR-TB strains were XDR [6]. In Latvia, 115 patients (19%) had XDR-TB, among 605 individuals with MDR-TB who initiated therapy during 2000–2002. As expected, treatment outcomes for patients with XDR-TB were poorer than for patients with MDR-TB [8]. Although international attention has been drawn to the emergence of XDR-TB,

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the data on clinical features including treatment outcomes, especially in non–HIV-infected patients with XDR-TB, are scarce. The aim of this study was to elucidate the clinical characteristics of XDR-TB and its impact on treatment outcomes among non–HIV-infected patients in low HIV-prevalent areas [9].

METHOD

Inclusion Criteria and Data Collection

The subjects included in the study received the diagnosis of and treatment as having MDR-TB at Seoul National University Hospital (Seoul, Republic of Korea), a university-affiliated tertiary care, referral hospital, between January 1996 and December 2005. We reviewed the medical records, microbiology results, other laboratory results, and radiographic results. Results of laboratory or radiographic examination performed at the time of diagnosis of MDR-TB were reviewed and analyzed. The protocol for this study was approved by the Ethical Review Committee of Seoul National University Hospital.

Treatment of Patients with MDR-TB

Although the treatment for these patients was individualized by each physician on the basis of drug-susceptibility testing, the principles of treatment for patients with MDR-TB in our institution were (1) use any first-line agents to which TB shows susceptibility, (2) use injectable anti-TB drugs and quinolones if susceptible, (3) add second-line bacteriostatic agents as needed to make up the 5-drug regimen, and (4) treat for 2 years after culture conversion. In addition, the general indication for surgical resection was MDR-TB refractory to at least 6 months of medical treatment with a primary localized lesion.

Definitions

TB definitions. MDR-TB was defined as TB caused by bacilli showing resistance to at least isoniazid and rifampicin. XDR-TB was defined as TB caused by bacilli showing resistance to isoniazid and rifampicin and also showing resistance to any

Table 1. Baseline clinical characteristics of 211 patients with multidrug-resistant tuberculosis (MDR-TB), including those with extensively drug-resistant tuberculosis (XDR-TB).

Characteristic	Total MDR-TB	XDR-TB	Non–XDR-TB	P[a]
All subjects	211 (100)	43 (20.4)	168 (79.6)	…
Age, median years (range)	37 (13–91)	35 (16–69)	39 (13–91)	.202
Male sex	124 (58.8)	22 (51.2)	102 (60.7)	.256
Mean body mass index[b] ± SD	19.9 ± 3.4	20.1 ± 3.8	19.9 ± 3.3	.831
Comorbidities				
All	72 (34.1)	10 (23.3)	62 (36.9)	.092
Diabetes	30 (14.2)	2 (4.7)	28 (16.7)	.044
Cardiovascular diseases	19 (9.0)	1 (2.3)	18 (10.7)	.132
Chronic liver diseases	13 (6.2)	3 (7.0)	10 (6.0)	.731
Chronic renal failure	2 (0.9)	1 (2.3)	1 (0.6)	.367
COPD	7 (3.3)	1 (2.3)	6 (3.6)	1.000
Malignancy	7 (3.3)	…	7 (4.2)	.349
Other[c]	23 (10.9)	4 (9.3)	19 (11.3)	1.000
Proportion of current/former smokers (%)	70/184 (38.0)	10/38 (26.3)	60/146 (41.1)	.095
Proportion of subjects with a family history of tuberculosis[d] (%)	51/168 (30.4)	14/37 (37.8)	37/131 (28.2)	.262
Primary drug resistance[e]	84 (39.8)	19 (44.2)	65 (38.7)	.511
Laboratory test, mean value ± SD				
Hematocrit, %	38.6 ± 4.7	38.3 ± 3.8	38.6 ± 4.8	.794
Protein, g/dL	7.4 ± 0.6	7.5 ± 0.5	7.4 ± 0.6	.459
Albumin, g/dL	3.9 ± 0.5	3.8 ± 0.4	3.9 ± 0.5	.783
Cholesterol, mg/dL	161.1 ± 34.7	162.0 ± 40.0	160.9 ± 33.8	.896
Radiographic finding				
Cavity	160 (75.8)	37 (86.0)	123 (73.2)	.099
Bilateral cavities	70 (33.2)	20 (46.5)	50 (29.8)	.042
Combined extrapulmonary tuberculosis	29 (13.7)	4 (9.3)	25 (14.9)	.343

NOTE. Data are no. (%) of patients, unless otherwise specified. COPD, chronic obstructive pulmonary disease.

[a] Comparison between patients with and without XDR-TB.
[b] Calculated as weight in kilograms divided by the square of height in meters.
[c] Other diseases included alcohol addiction, asthma, connective-tissue diseases, hematologic diseases, idiopathic pulmonary fibrosis, and glomerulonephritis.
[d] History of tuberculosis among first- and second-degree relatives.
[e] Patients with MDR-TB who had not received treatment with anti-tuberculosis drugs were classified as having primary resistance [14].

Table 2. Treatment modalities and adverse reactions among patients with multidrug-resistant tuberculosis (MDR-TB), including those with extensively drug-resistant tuberculosis (XDR-TB).

Characteristic	Total MDR-TB	XDR-TB	Non–XDR-TB	P^a
No. (%) of subjects	211 (100)	43 (20.4)	168 (79.6)	…
Duration of treatment, median months (range)	26 (1–136)	43 (3–132)	25 (1–136)	.003
Surgical resection	63 (29.9)	24 (55.8)	39 (23.2)	<.001
Mean no. of drugs used (range)	6 (3–12)	7 (4–12)	6 (3–11)	<.001
Treatment received				
Isoniazid	54 (25.6)	20 (46.5)	34 (20.2)	<.001
Rifamycins				.011
All	52 (24.6)	17 (39.5)	35 (20.8)	
Rifampicin	44 (20.9)	13 (30.2)	31 (18.5)	
Rifabutin	8 (3.8)	3 (7.0)	5 (3.0)	
Ethambutol	81 (38.4)	17 (39.5)	64 (38.1)	.862
Pyrazinamide	108 (51.2)	25 (58.1)	83 (49.4)	.307
Quinolones				.481
All	179 (84.8)	35 (81.4)	144 (85.7)	
Ofloxacin	32 (15.2)	12 (27.9)	20 (11.9)	
Levofloxacin	155 (73.5)	28 (65.1)	127 (75.6)	
Moxifloxacin	19 (9.0)	8 (18.6)	11 (6.5)	
Injectable anti-tuberculosis drugs				.070
All	165 (78.2)	38 (88.4)	127 (75.6)	
Streptomycin	89 (42.2)	22 (51.2)	67 (39.9)	
Kanamycin	83 (39.3)	18 (41.9)	65 (38.7)	
Capreomycin	6 (2.8)	4 (9.3)	2 (1.2)	
Tuberactinomycin	7 (3.3)	5 (11.6)	2 (1.2)	
Amikacin	5 (2.4)	2 (4.7)	3 (1.8)	
Para-aminosalicylic acid	161 (76.3)	36 (83.7)	125 (74.4)	.200
Cycloserine	192 (91.0)	38 (88.4)	154 (91.7)	.550
Prothionamide	175 (82.9)	37 (86.0)	138 (82.1)	.544
Amoxicillin-clavulanate	88 (41.7)	32 (74.4)	56 (33.3)	<.001
Macrolides				
All	72 (34.1)	23 (53.5)	49 (29.2)	.003
Clarithromycin	58 (27.5)	18 (41.9)	40 (23.8)	
Roxithromycin	15 (7.1)	6 (14.0)	9 (5.4)	
Linezolid	3 (1.4)	1 (2.3)	2 (1.2)	.497
IFN-γ	1 (0.5)	1 (2.3)	…	.204
Adverse drug reactions	54 (25.6)	15 (34.9)	39 (23.2)	.118
Ocular toxicity[b]	5 (2.4)	2 (4.7)	3 (1.8)	.270
Ototoxicity[b]	8 (3.8)	2 (4.7)	6 (3.6)	.667
Hepatotoxicity[c]	8 (3.8)	3 (7.0)	5 (3.0)	.208
Hematologic abnormalities[d]	2 (0.9)	…	2 (1.2)	1.000
Serious GI trouble[b]	14 (6.6)	4 (9.3)	10 (6.0)	.491
Hypothyroidism	14 (6.6)	3 (7.0)	11 (6.5)	1.000
Neurologic abnormalities[b]	9 (4.3)	3 (7.0)	6 (3.6)	.392
Allergic reaction[b]	6 (2.8)	2 (4.7)	4 (2.4)	.604

NOTE. Data are no. (%) of patients, unless otherwise specified. GI, gastrointestinal.

[a] Comparison between patients with and without XDR-TB.

[b] Included only if the adverse reactions prompted change or cessation of treatment medications.

[c] Hepatotoxicity was defined as a serum aspartate aminotransferase level >3 times the upper limit of normal in the presence of symptoms or >5 times the upper limit of normal in the absence of symptoms [15].

[d] Decrease of leukocyte or platelet count to less than the normal lower limit.

Table 3. Treatment outcomes among patients with multidrug-resistant tuberculosis (MDR-TB), including those with extensively drug-resistant tuberculosis (XDR-TB).

Treatment outcome	No. (%) of patients with treatment outcome		
	Total MDR-TB (n = 211)	XDR-TB (N = 43)	Non–XDR-TB (N = 168)
Treatment success			
All	132 (62.6)	23 (53.5)	109 (64.9)
Cure	107 (50.7)	23 (53.5)	84 (50.0)
Completed	25 (11.8)	…	25 (14.9)
Treatment failure			
All	65 (30.8)	19 (44.2)	46 (27.4)
Relapse	6 (2.8)	2 (4.7)	4 (2.4)
Failure	40 (19.0)	11 (25.6)	29 (17.3)
Death	19 (9.0)	6 (14.0)	13 (7.7)
Other[a]			
All	14 (6.6)	1 (2.3)	13 (7.7)
Default	7 (3.3)	1 (2.3)	6 (3.6)
Transfer out	7 (3.3)	…	7 (4.2)A

NOTE. P = .057 from comparison of treatment success and treatment failure by χ^2 test between XDR-TB and non–XDR-TB.

[a] Excluded from further analysis.

fluoroquinolone and to any of the following 3 injectable anti-TB drugs: capreomycin, kanamycin, and amikacin [10].

Treatment outcomes. The treatment outcomes were classified in accordance with the suggested criteria of Laserson et al. [11]. A patient was considered "cured" if he or she completed treatment according to the country's protocol and was consistently culture negative (with at least 5 results) during the final 12 months of treatment. If only 1 positive culture result was reported during that time and there was no concomitant clinical evidence of deterioration, a patient might still be considered cured, provided that the positive culture result was followed by a minimum of 3 consecutive negative culture results for samples obtained at least 30 days apart. If the patient completed treatment but did not meet the definition for cure or had treatment failure because of lack of bacteriologic results, the treatment was considered "completed" for the patient. Treatment was regarded as successful for patients considered "cured" or "completed." If a cured patient or a patient who completed therapy resumed treatment >6 months after completion of the first treatment because of the emergence of MDR-tuberculous bacilli, the patient was classified as having a disease "relapse." "Failure" was defined as ⩾2 of 5 positive culture results recorded during the final 12 months or any 1 of the final 3 cultures being positive. Patients with "relapse" or "failure" were regarded as the treatment-failure group. In addition, we also included patients who died during the course of MDR-TB treatment in the failure group. "Default" was defined as a patient who missed >2 consecutive scheduled visits, for any reason.

Statistical Analysis

Data are expressed as median values or means ± SDs. Comparisons of demographic characteristics, laboratory results, and radiographic findings between patients with and without XDR-TB were performed using Pearson's χ^2 test or Fisher's exact test for categorical variables and Student's t test for continuous variables. To elucidate the predictors for treatment failure, we compared selected clinical variables between treatment success and failure through univariate comparison and subsequent multiple logistic regression. In regression, backward elimination was used to select variables to be maintained in the final model, with use of a P value of <.10 as the criterion for statistical significance of association. The area under the receiver operator characteristic curve was used to evaluate the performance of the models. All statistical analyses were performed with SPSS software, version 11.0 (SPSS).

RESULTS

Baseline clinical characteristics of patients with MDR-TB or XDR-TB. Between January 1996 and December 2005, 212 patients received a diagnosis of and treatment for MDR-TB at Seoul National University Hospital. Of those, 1 patient was excluded from further analysis because of anti-HIV antibody seropositivity. The clinical data for patients with MDR-TB who underwent surgical resection were published previously [12, 13].

A total of 211 non–HIV-infected patients with MDR-TB were included in the final analysis. Among them, 43 patients (20.4%) had XDR-TB. Their median age was 35 years (range, 16–69 years); 22 patients (51.2%) were male. There was no significant difference between patients with XDR-TB and patients unaffected with MDR-TB, in terms of body mass index, comorbidities, history of smoking, family history of TB, and laboratory findings. However, the presence of bilateral cavities at the time of diagnosis of MDR-TB was more common in patients with XDR-TB (46.5% vs. 29.8%; P = .042) (table 1).

Treatment modalities and adverse reactions. The median duration of treatment was 43 months (range, 3–132 months) in patients with XDR-TB and 25 months (range, 1–136 months) in patients with non–XDR-TB (P = .003). The median number of anti-TB drugs used was higher in patients with XDR-TB (7 vs. 6 drugs; P < .001). In addition, surgical resection was performed more frequently in patients with XDR-TB (55.8% vs. 23.2%; P < .001). The use of isoniazid (P < .001) and rifamycins (P = .011) was more common in patients with XDR-TB. The rates of serious adverse drug reactions were not different between the 2 groups (P = .118) (table 2). The usual doses of anti-TB drugs in our institution were included in our previous report [1].

Treatment outcomes. Among a total of 211 patients with MDR-TB, 107 patients (50.7%) were considered cured, and

Table 4. Predictors of treatment failure among patients with multidrug-resistant tuberculosis.

Variable	Treatment success (n = 132)	Treatment failure (n = 65)	Univariate analysis		Multivariate analysis	
			OR[b] (95% CI)	P	OR[b] (95% CI)	P
Age, mean years ± SD	37.9 ± 16.0	41.0 ± 15.5	1.01 (0.99–1.03)	.20	…	…
Male sex	76 (57.6)	39 (60.0)	1.11 (0.60–2.02)	.75	…	…
Mean body mass index[a] ± SD	20.1 ± 3.4	19.1 ± 3.7	0.92 (0.82–1.03)	.14	…	…
Comorbidity	43 (32.6)	25 (38.5)	1.29 (0.70–2.40)	.42	2.62 (1.00–6.87)	.05
Current or former smokers	40 (35.1)	27 (46.6)	1.61 (0.85–3.07)	.15	…	…
Family history of TB	34 (31.8)	15 (29.4)	0.89 (0.43–1.85)	.76	…	…
Primary drug resistance	55 (41.7)	24 (36.9)	0.82 (0.45–1.51)	.52	…	…
Extensive drug resistance	23 (17.4)	19 (29.2)	1.96 (0.97–3.94)	.06	4.46 (1.35–14.74)	.01
Laboratory test, mean value ± SD						
Hematocrit, %	38.8 ± 4.4	36.9 ± 5.4	0.91 (0.83–1.00)	.05	…	…
Protein, g/dL	7.4 ± 0.6	7.3 ± 0.7	0.65 (0.34–1.24)	.19	…	…
Albumin, g/dL	3.9 ± 0.5	3.7 ± 0.3	0.23 (0.08–0.62)	.002	0.87[c] (0.77–0.97)	.01
Cholesterol, mg/dL	160.6 ± 34.6	154.7 ± 30.1	0.99 (0.98–1.01)	.41	…	…
Radiographic findings						
Cavity	96 (73.3)	54 (84.4)	1.97 (0.90–4.29)	.08	…	…
Bilateral cavities	32 (24.4)	35 (54.7)	3.73 (1.98–7.03)	<.001	2.42 (0.95–6.19)	.06
Combined extrapulmonary TB	17 (12.9)	11 (16.9)	1.38 (0.60–3.14)	.45	…	…
Surgical resection	43 (32.6)	17 (26.2)	1.36 (0.70–2.65)	.36	…	…

NOTE. Data are no. (%) of patients, unless otherwise specified. Analysis was performed after exclusion of 7 defaulted and 7 transferred-out patients. TB, tuberculosis.

[a] Calculated as weight in kilograms divided by the square of height in meters.

[b] For treatment failure.

[c] (× + 0.10 g/dL vs. × g/dL).

treatment of 25 (11.8%) was considered completed. The overall rate of treatment success was 62.5%. In patients with XDR-TB, the overall treatment failure rate was 44.2% (19 patients), whereas 27.4% of patients (46 patients) with non–XDR-TB failed to be cured ($P = .057$) (table 3).

Impact of XDR on treatment outcomes. On the basis of the clinical variables included in univariate comparison between the treatment success and failure groups, the final multiple logistic regression model predicting treatment failure included XDR, presence of comorbidities, level of albumin, and the presence of bilateral cavities. Among these variables, the presence of XDR (adjusted OR, 4.46; 95% CI, 1.35–14.74) and underlying comorbidity (adjusted OR, 2.62; 95% CI, 1.00–6.87) were independent risk factors for treatment failure. However, a higher level of albumin was inversely associated with treatment failure (adjusted OR, 0.87; 95% CI, 0.77–0.97) (table 4). The fitness of the final model was good (area under the receiver operator characteristic curve, 0.79; 95% CI, 0.71–0.88).

DISCUSSION

Through this study involving 211 HIV-seronegative patients with MDR-TB, we showed that the treatment failure rate is 44.2% for patients with XDR-TB. The treatment failure rate for patients with MDR-TB but not XDR-TB was 27.4%. The adjusted OR of XDR on treatment failure was 4.46 (95% CI, 1.35–14.74).

Although the concept of XDR-TB as a poor prognostic factor was only recently introduced [6], ofloxacin resistance among patients with MDR-TB has been regarded as an independent poor prognostic factor in previous reports [13, 16, 17]. In addition, the injectable anti-TB drugs, including streptomycin, kanamycin, amikacin, and capreomycin, are pivotal agents in the treatment of MDR-TB [18–20]. In this context, the prognosis for patients with MDR-TB with additional resistance to quinolones and injectable anti-TB drugs is expected to be poorer than that for patients without additional resistance [6]. In this study, patients with XDR-TB showed 4.46 times the treatment failure risk of patients with non–XDR-TB, despite the facts that surgical resection was performed more frequently and that more anti-TB drugs were used for longer periods in treatment of patients with XDR-TB. A much higher risk of treatment failure in them suggests that patients with XDR-TB should be regarded as having a poor prognosis among both HIV-infected and -uninfected patients with MDR-TB.

In this study, the patients with XDR-TB received treatment with more anti-TB drugs (7 vs. 6 drugs; $P < .001$) for a longer period (43 vs. 25 months; $P = .003$) than did patients with non-XDR TB. In addition, surgical resection was performed

more frequently for patients with XDR-TB (55.8% vs. 23.2%; $P < .001$). The worse response to anti-TB treatment in patients with XDR-TB prompted physicians to use more drugs for a longer period and to try surgical resection of the diseased tissue, even in patients without a high probability of success. Furthermore, isoniazid ($P < .001$) and rifamycins ($P = .011$) were more frequently prescribed for patients with XDR-TB than for patients with simple MDR-TB. For many of our study patients with XDR-TB, it was impossible to create a regimen that included 4 or 5 drugs, which is recommended for treatment of patients with MDR-TB [18–20]; therefore, for those patients for whom only 2 or 3 susceptible drugs were available, we frequently created a 4- or 5-drug regimen by adding isoniazid and rifampicin.

Hypoalbuminemia is generally regarded as a marker of poor nutritional status in patients with TB [21, 22]. In this study, the level of serum albumin at the time of diagnosis of MDR-TB, but not body mass index, was associated with treatment outcomes. Previous studies showed that hypoalbuminemia-protein malnutrition itself could impair host immunity against *Mycobacterium tuberculosis* through decreased production of cytokines, including IFN-γ [23], or the reduction of CD4 and CD8 T cell numbers observed in animal models [24]. The fact that a higher level of serum albumin was inversely related with treatment failure in patients with XDR-TB could be explained in this context.

Although the emergence of XDR-TB threatens to return TB treatment to the preantibiotic era, no breakthrough for the treatment of XDR-TB has been reported yet. While trying to make progress on new drug development or new combinations of existing anti-TB drugs, the importance of standardizing the TB-treatment strategy, improving case detection rate, decreasing rates of treatment default, and sufficient political will and financial support should be stressed for the control of XDR-TB [5].

In conclusion, the presence of XDR was an independent poor prognostic factor in non–HIV-infected patients with MDR-TB. The presence of comorbidity and the level of serum albumin at the time of diagnosis of MDR-TB were also associated with treatment outcomes.

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References

1. Kang YA, Choi YJ, Cho YJ, et al. Cost of treatment for multidrug-resistant tuberculosis in South Korea. Respirology **2006**; 11:793–8.
2. Iseman MD. Treatment of multidrug-resistant tuberculosis. N Engl J Med **1993**; 329:784–91.
3. Dye C, Espinal MA, Watt CJ, Mbiaga C, Williams BG. Worldwide incidence of multidrug-resistant tuberculosis. J Infect Dis **2002**; 185: 1197–202.
4. Goble M, Iseman MD, Madsen LA, Waite D, Ackerson L, Horsburgh CR Jr. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. N Engl J Med **1993**; 328:527–32.
5. Dukes Hamilton C, Sterling TR, Blumberg HM, et al. Extensively drug-resistant tuberculosis: are we learning from history or repeating it? Clin Infect Dis **2007**; 45:338–42.
6. Centers for Disease Control and Prevention. Emergence of *Mycobacterium tuberculosis* with extensive resistance to second-line drugs—worldwide, 2000–2004. MMWR Morb Mortal Wkly Rep **2006**; 55: 301–5.
7. Raviglione M. XDR-TB: entering the post-antibiotic era? Int J Tuberc Lung Dis **2006**; 10:1185–7.
8. Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet **2006**; 368:1575–80.
9. Oh MD, Choe K. Epidemiology of HIV infection in the Republic of Korea. J Korean Med Sci **1999**; 14:469–74.
10. World Health Organization. Extensively drug-resistant tuberculosis (XDR-TB): recommendations for prevention and control. Wkly Epidemiol Rec **2006**; 81:430–2.
11. Laserson KF, Thorpe LE, Leimane V, et al. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis **2005**; 9:640–5.
12. Sung SW, Kang CH, Kim YT, Han SK, Shim YS, Kim JH. Surgery increased the chance of cure in multi-drug resistant pulmonary tuberculosis. Eur J Cardiothorac Surg **1999**; 16:187–93.
13. Kim HJ, Kang CH, Kim YT, et al. Prognostic factors for surgical resection in patients with multidrug-resistant tuberculosis. Eur Respir J **2006**; 28:576–580.
14. World Health Organization. Guidelines for the management of drug-resistant tuberculosis. Geneva: World Health Organization, **1997**.
15. Blumberg HM, Burman WJ, Chaisson RE, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med **2003**; 167:603–62.
16. Leimane V, Riekstina V, Holtz TH, et al. Clinical outcome of individualised treatment of multidrug-resistant tuberculosis in Latvia: a retrospective cohort study. Lancet **2005**; 365:318–26.
17. Yew WW, Chan CK, Chau CH, et al. Outcomes of patients with multidrug-resistant pulmonary tuberculosis treated with ofloxacin/levofloxacin-containing regimens. Chest **2000**; 117:744–51.
18. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: World Health Organization, **2006**.
19. Caminero JA. Management of multidrug-resistant tuberculosis and patients in retreatment. Eur Respir J **2005**; 25:928–36.
20. Mukherjee JS, Rich ML, Socci AR, et al. Programmes and principles in treatment of multidrug-resistant tuberculosis. Lancet **2004**; 363: 474–81.
21. Karyadi E, Schultink W, Nelwan RH, et al. Poor micronutrient status of active pulmonary tuberculosis patients in Indonesia. J Nutr **2000**; 130:2953–8.
22. Onwubalili JK. Malnutrition among tuberculosis patients in Harrow, England. Eur J Clin Nutr **1988**; 42:363–6.
23. Dai G, McMurray DN. Altered cytokine production and impaired antimycobacterial immunity in protein-malnourished guinea pigs. Infect Immun **1998**; 66:3562–8.
24. Mainali ES, McMurray DN. Protein deficiency induces alterations in the distribution of T-cell subsets in experimental pulmonary tuberculosis. Infect Immun **1998**; 66:927–31.

Two errors appeared in the 1 September 2007 issue of the journal (Daar ES, Kesler KL, Petropoulos CJ, Huang W, Bates M, Lail AE, Coakley EP, Gomperts ED, Donfield SM, for the Hemophilia Growth and Development Study. Baseline HIV type 1 coreceptor tropism predicts disease progression. Clin Infect Dis 2007; 45:643–9). The end of the fourth sentence of the first paragraph of the Statistical Analysis section should read: "… as well as first-order interactions with study visit number and baseline $CD4^+$ T cell count and study visit number and coreceptor tropism" (*not* "… as well as first-order interactions with study visit number"). Also, consistent with what is stated in the text of the Results section, footnote *b* in table 1 should refer to both "$CD4^+$ T cell count, cells/uL" and "Plasma HIV-1 RNA level, $\log_{10}$ copies/mL" but should not refer to "Estimated duration of HIV-1 infection, years." The corrected table appears below. The authors regret these errors.

Table 1. Characteristics of patients at the time of tropism assessment.

Characteristic	Patients with CCR5-tropic virus (n = 75)	Patients with dual or mixed tropic virus[a] (n = 51)
Age, years	13.8 ± 3.2	13.7 ± 2.5
Estimated duration of HIV-1 infection, years	7.50 ± 1.23	7.15 ± 1.48
$CD4^+$ T cell count, cells/μL[b]	449 ± 262	200 ± 259
Plasma HIV-1 RNA level, $\log_{10}$ copies/mL[b]	3.50 ± 0.46	3.95 ± 0.60

NOTE. Data are mean ± SD.

[a] CCR5-tropic and CXCR4-tropic.

[b] $P < .001$.

An error appeared in the 15 November 2007 issue of the journal (Kim H-R, Hwang SS, Kim HJ, Lee SM, Yoo C-G, Kim YW, Han SK, Shim Y-S, Yim J-J. Impact of extensive drug resistance on treatment outcomes in non–HIV-infected patients with multidrug-resistant tuberculosis. Clin Infect Dis 2007; 45: 1290–5). The institutional affiliation for Hye-Ryoun Kim, Hyun Ji Kim, Sang Min Lee, Chul-Gyu Yoo, Young Whan Kim, Sung Koo Han, Young-Soo Shim, and Jae-Joon Yim should be Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine and Lung Institute, Seoul National University College of Medicine, Seoul, Republic of Korea (*not* Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine and Lung Institute, Korea Centers for Disease Control and Prevention, Seoul, Republic of Korea). The authors regret this error.

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