MULTI-DRUG RESISTANT TB AND HIV IN THAILAND: OVERLAPPING, BUT NOT INDEPENDENTLY ASSOCIATED RISK FACTORS

Somsak Akksilp[1], Wanpen Wattanaamornkiat[1], Wanitchaya Kittikraisak[2], Sriprapa Nateniyom[3], Somsak Rienthong[3], Chawin Sirinak[4], Keerataya Ngamlert[4], Wiroj Mankatittham[5], Wanchai Sattayawuthipong[6], Surin Sumnapun[7], Norio Yamada[8], Patama Monkongdee[2], Amornrat Anuwatnonthakate[2], Channawong Burapat[2], Charles D Wells[9], Jordan W Tappero[9] and Jay K Varma[2,9]

[1]Office of Disease Prevention and Control 7, Ubon Ratchathani; [2]Thailand Ministry of Public Health – US Centers for Disease Control and Prevention Collaboration, Nonthaburi; [3]Thailand Ministry of Public Health, Nonthaburi; [4]Department of Health, Bangkok Metropolitan Administration, Bangkok; [5]Bamrasnaradura Infectious Diseases Institute, Nonthaburi; [6]Phuket Provincial Health Office, Phuket; [7]Chiang Rai Provincial Health Office, Chiang Rai, Thailand; [8]Research Institute of Tuberculosis, Tokyo, Japan; [9]US Centers for Disease Control and Prevention, Atlanta, USA

Abstract. The HIV and multi-drug resistant tuberculosis (MDR-TB) epidemics are closely linked. In Thailand as part of a sentinel surveillance system, we collected data prospectively about pulmonary TB cases treated in public clinics. A subset of HIV-infected TB patients identified through this system had additional data collected for a research study. We conducted multivariate analysis to identify factors associated with MDR-TB. Of 10,428 TB patients, 2,376 (23%) were HIV-infected; 145 (1%) had MDR-TB. Of the MDR-TB cases, 52 (37%) were HIV-infected. Independent risk factors for MDR-TB included age 18-29 years old, male sex, and previous TB treatment, but not HIV infection. Among new patients, having an injection drug use history was a risk factor for MDR-TB. Of 539 HIV-infected TB patients in the research study, MDR-TB was diagnosed in 19 (4%); the only significant risk factors were previous TB treatment and previous hepatitis. In Thailand, HIV is common among MDR-TB patients, but is not an independent risk factor for MDR-TB. Populations at high risk for HIV–young adults, men, injection drug users – should be prioritized for drug susceptibility testing.

INTRODUCTION

Drug-resistant tuberculosis (TB) has emerged as an important global public health threat. The World Health Organization (WHO) estimates that 489,000 cases of multi-drug resistant TB (MDR-TB), defined as infection with a *Mycobacterium tuberculosis* (MTB) strain resistant to at least isoniazid (INH) and rifampin, occur annually, predominantly in Eastern Europe and Asia (WHO/IUATLD, 2008). MDR-TB is difficult to diagnose and treat. Diagnosis requires sophisticated laboratories that can perform

Correspondence: Dr Jay K Varma, CDC, US Embassy Beijing, No. 55, An Jia Lou Road, Beijing 100600, People's Republic of China.
Tel: +86 (10) 6532-9901; Fax: +86 (10) 6532-9908
E-mail: jvarma@cdc.gov

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mycobacterial culture and drug-susceptibility testing (DST) or polymerase chain reaction (PCR)-based testing for genetic mutations associated with resistance. Treatment involves prolonged use of "second-line" anti-TB drugs that are less effective, less tolerated, more toxic, and more expensive than "first-line" anti-TB medications (WHO, 2006). Under optimum program conditions, cure rates for drug-susceptible TB exceed 90%; for MDR-TB, cure rates infrequently exceed 70% (Nathanson *et al*, 2006). Inadequate treatment of MDR-TB can select for even more lethal strains of MDR-TB, such as extensively drug-resistant TB, which have substantially lower cure rates (Dorman and Chaisson, 2007).

For epidemiologic and biological reasons, the HIV epidemic is closely linked to the problem of MDR-TB. The HIV epidemic has resulted in a dramatic increase in the number of TB cases occurring globally, because HIV is the most potent risk factor for TB disease (Corbett *et al*, 2006). In many countries, rising case numbers, without proportional increases in TB program resources, have led to less rigorous TB case management, increasing the risk of selecting for MDR-TB (Corbett *et al*, 2006). There is overlap between the populations at risk for HIV and MDR-TB; for example, persons who are incarcerated or who work in health care facilities are often at high risk for MDR-TB and HIV infection (Pearson *et al*, 1992; Valway *et al*, 1994; Wilkinson and Gilks, 1998; Dolan *et al*, 2007). Sub-therapeutic levels of anti-TB drugs, which can select for drug-resistant MTB, may occur in HIV-infected TB patients, because of malabsorption, drug-drug interactions between TB and HIV medications, and overlapping toxicity between TB and HIV medications that leads to selective drug ingestion (Burman, 2005). Most notably, HIV patients appear uniquely susceptible to acquiring and dying from MDR-TB (Ghandi *et al*, 2006; Wells *et al*, 2007).

Despite the apparent confluence of the HIV and MDR-TB epidemics, data have been conflicting about whether HIV infection is actually a risk factor for MDR-TB (Wells *et al*, 2007). Most data about the interaction between these epidemics come from special projects conducted in selected cities or referral centers. Ideal data sources would include continuous population-based surveillance of drug-resistance and HIV at the national level, continuous surveillance in sentinel sites, or periodic surveys. Such studies, however, are rare. For example, only four countries with either MDR-TB or HIV epidemics, only four studies have reported the rate of HIV among MDR-TB patients and only two have reported the rate of MDR-TB among HIV-infected TB patients (Wells *et al*, 2007). The WHO has, therefore called on countries to conduct studies to assess the interaction between the MDR-TB and HIV epidemics (WHO, 2007).

Thailand is one of 22 WHO-designated high-burden TB countries, and an estimated 15-20% of TB cases are associated with HIV (WHO, 2007; Nateniyom, 2008). A nationally representative drug-resistance survey conducted in 2006 found the rate of MDR-TB was 1.7% in new patients and 34.5% in previously treated patients; data regarding the HIV status of these patients were not collected (Jittimanee *et al*, 2009). To determine whether HIV is a risk factor for MDR-TB, we analyzed data from a surveillance system that prospectively collects detailed data for all TB cases diagnosed in four high HIV prevalence provinces. To identify risk factors for MDR-TB, specifically among HIV-infected TB patients, we analyzed data from an observational cohort study that was nested within the surveillance system.

MATERIALS AND METHODS

Surveillance system

As part of a demonstration project

known as the Thailand TB Active Surveillance Network, standardized data were collected prospectively from all TB patients treated in selected parts of Thailand: all districts in Ubon Ratchathani, Phuket, and Chiang Rai Provinces; 9 districts in Bangkok; and the National Infectious Diseases Hospital in Nonthaburi Province, beginning in 2004. Excluding the National Infectious Diseases Referral Hospital, which has no base population, the population of the study area was 3.1 million persons. Public health staff collected data prospectively from routine medical records and recorded data in an electronic database. A detailed description of methods has been published separately (Varma *et al*, 2007).

The surveillance system underwent ethical review by the Thailand Ministry of Public Health (MOPH) and US Centers for Disease Control and Prevention (US CDC). It was determined to be public health program implementation, not human subjects research.

Observational research study

From May 2005 to September 2006, HIV-infected TB patients from the surveillance area, except for Chiang Rai, were offered enrollment in a prospective cohort study (Varma *et al*, 2009) (Fig 1). Patients were eligible if they were HIV-infected, non-pregnant, non-incarcerated, aged ≥18 years, and previously untreated for TB or treated for less than four weeks before study enrollment. Patients consenting to study enrollment received usual care for TB, HIV, and other diseases according to the physicians' discretion. We followed patients from initiation to the end of TB treatment. At the beginning of treatment, clinical staff examined patients and interviewed them using standardized study forms that asked about demographic characteristics, past and

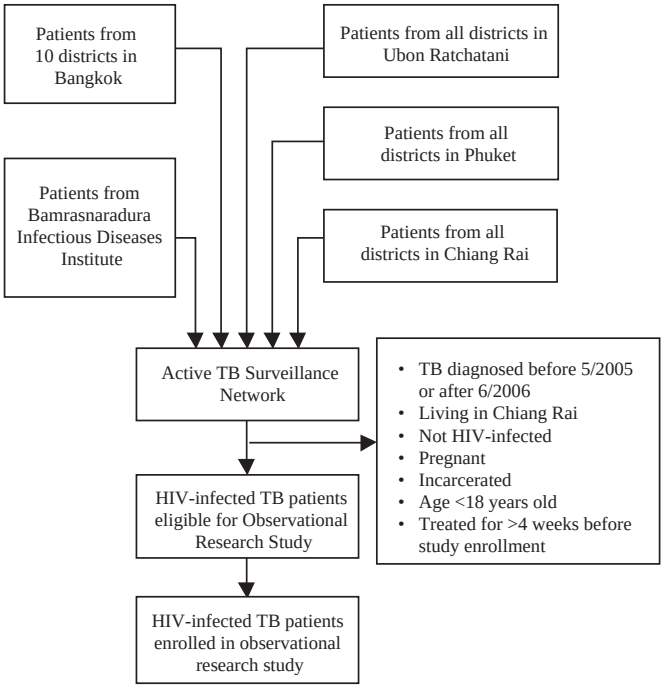

Fig 1–Flow of surveillance and observational research study.

present medical history, knowledge and attitudes related to TB and HIV, and sex and drug use history. Blood samples were tested for serum chemistry, liver function enzymes, complete blood count, viral hepatitis, and CD4+ T-lymphocyte (CD4) count.

The observational study was approved by the human subjects research ethical review committees of the Thailand MOPH, US CDC, and Bangkok Metropolitan Administration.

TB and MDR-TB diagnosis

For both surveillance and the observational research study, patients diagnosed with pulmonary TB provided sputum specimens for smear microscopy. We encouraged, but did not require, that facilities collect three sputum specimens from all patients. Unprocessed sputum was examined at the TB clinics using the Ziehl-Neelsen acid-fast stain method. We also encouraged, but did not require, that at least one sputum specimen be sent for mycobacterial culture, identification, and drug-susceptibility testing. Mycobacterial culture was performed at one laboratory in each province using solid (Ogawa in one site; Lowenstein-Jensen in all others) and mycobacterial growth indicator tube (MGIT) media, according to standard methods (Isenberg, 1992). Identification and DST for INH, rifampin, ethambutol, and streptomycin were performed at the national TB reference laboratory or the Bangkok TB laboratory using MGIT.

Statistical analysis

We analyzed data from patients registered in surveillance from October 2004 to September 2006 and for all patients in the observational study. We excluded patients with exclusively extra-pulmonary TB, because few cases were microbiologically confirmed and therefore eligible for DST. We also excluded patients who were less than 18 years old, because they were not eligible for enrollment in the observational study.

For both surveillance and the observational study, we calculated proportions to describe demographic characteristics and clinical features of patients with and without MDR-TB. We analyzed all patients and the subset of new (previously untreated) TB patients. Covariates were categorized in the same manner when possible. Due to the small number of MDR-TB patients in the observational study, combined categories were used for some covariates, *eg*, age and registration status, to make our multivariable models more stable. We defined a two-sided p-value of ≤ 0.05 as statistical significance and performed all analyses using Stata software version 8.0 (StataCorp LP, College Station, TX, USA).

Handling of missing data. To account for missing data, we conducted two analyses. In the first analysis, we excluded patients with unknown MDR-TB status. In the second analysis, we assumed that patients with unknown MDR-TB status did not have MDR TB. In both analyses, we first identified factors associated with MDR-TB at $p \leq 0.20$ in univariate analysis, checked them for co-linearity and constructed two-way interaction terms as products of covariates. Next, we fitted a parsimonious multivariate logistic regression model by including covariates and their interaction terms in the model, using backward stepwise variable selection technique, and assessing model fitness using the Hosmer and Lemeshow goodness-of-fit test. None of the interaction terms were found statistically significant.

To account for missing data in the surveillance system analysis, we also performed an analysis using multiple imputation. In this analysis, we imputed missing data for patient characteristics and MDR-TB and HIV infection status based on a probability model of the complete data, assuming multivariate normal distribution (Greenland and

Table 1
Characteristics and clinical features at time of TB diagnosis of pulmonary TB patients ≥18 years old in the Thailand TB active surveillance network, Thailand (2004-2006).

Characteristics and clinical features	All patients (*n*=10,428)	MDR-TB patients (*n*=145)	Non MDR-TB patients[a] (*n*=10,283)
	N (%)	*n* (%)	*n* (%)
Age (years)			
18-29	2,335 (22)	18 (12)	2,319 (23)
30-39	1,458 (14)	20 (14)	1,438 (14)
40-49	2,059 (20)	30 (21)	2,029 (20)
50-59	2,504 (24)	38 (26)	2,466 (24)
≥60	2,072 (20)	39 (27)	2,033 (20)
Male	7,056 (68)	113 (78)	6,943 (68)
Single			
Yes	2,490 (24)	41 (28)	2,449 (24)
No or unknown	7,938 (76)	104 (72)	7,834 (76)
Thai nationality			
Yes	9,618 (92)	133 (92)	9,485 (92)
No or unknown	810 (8)	12 (8)	798 (8)
Received standard HRZE regimen			
Yes	9,037 (87)	69 (48)	8,968 (88)
No or unknown	1,391 (13)	76 (54)	1,315 (12)
Smear positive			
Yes	6,175 (64)	122 (86)	6,053 (64)
No or unknown	4,253 (36)	23 (14)	4,330 (36)
Registered as new case	8,543 (82)	59 (41)	8,484 (83)
Live in migrant or refugee camp			
Yes	142 (1)	2 (1)	140 (1)
No or unknown	10,275 (99)	143 (99)	10,132 (99)
Mobile population[b]			
Yes	3,261 (30)	44 (30)	3,305 (30)
No or unknown	7,123 (70)	101 (70)	7,022 (70)
Live in municipal area			
Yes	4,581 (44)	77 (53)	4,504 (44)
No or unknown	5,851 (56)	62 (47)	5,779 (56)
Live in a crowded household[c]	4,068 (39)	48 (33)	4,020 (39)
Previously diagnosed with diabetes			
Yes	429 (4)	9 (6)	429 (4)
No or unknown	9,999 (96)	136 (94)	9,863 (96)
History of injection drug use			
Yes	329 (3)	14 (9)	315 (3)
No or unknown	10,085 (97)	134 (91)	9,951 (97)
HIV status			
Infected	2,376 (23)	52 (36)	2,324 (23)
Uninfected	5,560 (53)	74 (51)	5,486 (53)
Unknown	2,492 (24)	19 (13)	2,473 (24)

Table 1 (Continued)

Characteristics and clinical features	All patients (*n*=10,428)	MDR-TB patients (*n*=145)	Non MDR-TB patients[a] (*n*=10,283)
	N (%)	*n* (%)	*n* (%)
Abnormal chest x-ray			
Yes	9,103 (91)	126 (89)	8,977 (91)
No or unknown	1,325 (9)	19 (11)	1,306 (9)
CD4+ T-lymphocyte <100 cells/μl[d]			
Yes	1,151 (67)	28 (70)	1,123 (67)
No	570 (33)	12 (30)	558 (33)

TB, tuberculosis; HIV, human immunodeficiency virus; MDR-TB, multi-drug resistant tuberculosis; HRZE, isoniazid, rifampin, pyrazinamide, and ethambutol.
Only main characteristics and clinical features were shown
[a]Those with unknown multi-drug resistant TB status were assumed not to have multi-drug resistant TB
[b]Mobile defined as not living in the same district for 3 of the past 6 months
[c]Total individuals living in the same house ≥4
[d]Among HIV-infected patients with available CD4+ T-lymphocyte counts

Finkle, 1995; Donders *et al*, 2006). We performed five imputations using NORM version 2.03, resulting in five imputed datasets (Darmawan, 2002; Schafer, 2009). For each imputed dataset, we performed multivariate analysis as described above. After identifying covariates that were significant at $p \leq 0.05$ with the multivariate model for each imputed dataset, these five models were refitted to include all the covariates regardless of whether they were significant in the respective datasets for the purpose of retrieving the combined estimates. We combined estimates and standard errors from five analyses into a single set of results using Rubin's rules for scalar estimands (Rubin, 1987). We did not impute data for the observational study, because the dataset was relatively small and complete.

RESULTS

Characteristics of patients in the surveillance and the observational study

After excluding patients age <18 years old, extra-pulmonary TB patients, and patients whose TB diagnosis changed after registration, we analyzed data from 10,428 patients in the surveillance. Most patients were Thai men with a median age of 42 years [interquartile range (IQR), 31-57]; other characteristics are shown in Table 1. Most (82%) were new TB cases, and 64% were smear-positive. HIV infection was diagnosed in 23%; 53% were HIV-uninfected and 24% had unknown HIV status. Of 2,376 HIV-infected patients with known CD4 counts, 67% had a CD4 count <100 cells/μl. Characteristics of the 539 patients analyzed in the observational study are shown in Table 2. HIV-infected TB patients in the observational study were broadly similar to the HIV-infected TB patients in the surveillance study, except that the proportion of patients in the observational study that were previously treated was lower than in the surveillance study (14% *vs* 30%, $p<0.01$).

MDR-TB and HIV

In the surveillance, DST was performed in 3,235 (31%) patients. MDR-TB

Table 2
Characteristics and clinical features at time of TB diagnosis of HIV-infected pulmonary TB patients age ≥18 years old and enrolled in the observational study, Thailand (2005-2006).

Characteristics and clinical features	All patients (*n*=539)	MDR-TB patients (*n*=19)	Non MDR-TB patients[a] (*n*=520)
	N (%)	*n* (%)	*n* (%)
Characteristics			
Age (years)			
18-29	125 (23)	6 (32)	119 (23)
30-39	257 (48)	10 (53)	247 (48)
≥40	157 (29)	3 (16)	154 (30)
Male	399 (74)	14 (74)	385 (74)
Employed	320 (59)	12 (63)	308 (59)
Finished primary school	205 (38)	7 (37)	198 (38)
Single	178 (33)	9 (47)	169 (33)
Hospitalized at enrollment	124 (23)	6 (32)	118 (23)
Received HRZE regimen	448 (83)	12 (63)	436 (84)
Smear positive[b]	335 (66)	18 (95)	317 (65)
Registered as a new case	461 (86)	12 (63)	449 (86)
Incarceration history	240 (45)	11 (58)	229 (44)
Abnormal chest x-ray[b]	481 (95)	15 (94)	466 (95)
Self-reported history of hepatitis or cirrhosis	21 (4)	4 (21)	17 (3)
Diagnosed with HIV >30 days before TB diagnosis	196 (36)	12 (63)	194 (37)
Delay in TB diagnosis[c]	285 (53)	9 (47)	276 (53)
TB knowledge, attitudes, and beliefs			
High TB stigma score	366 (68)	11 (58)	355 (68)
Low TB knowledge score	108 (20)	7 (37)	101 (19)
Laboratory studies			
Reactive for hepatitis B antigen	49 (9)	4 (21)	45 (9)
Reactive for hepatitis C antibody	195 (36)	9 (47)	186 (36)
Abnormal liver enzyme level[d]	88 (16)	7 (37)	81 (15)
Abnormal hemoglobin level	245 (45)	9 (47)	236 (45)
CD4+ T-lymphocytes <100 cells/µl[b]	331 (63)	14 (74)	317 (62)
Drug use history			
Currently smoke	146 (27)	6 (32)	140 (27)
History of alcohol use	392 (73)	16 (84)	376 (72)
History of methamphetamine use	242 (45)	11 (58)	231 (45)
History of marijuana use	212 (39)	9 (47)	203 (39)
History of injection drug use	160 (30)	9 (47)	151 (29)

TB, tuberculosis; HIV, human immunodeficiency virus; MDR-TB, multi-drug resistant tuberculosis; HRZE, isoniazid, rifampin, pyrazinamide, and ethambutol

[a]Those with unknown multi-drug resistant TB status were assumed not to have multi-drug resistant TB

[b]Those with available results only

[c]Having a cough lasting greater than one month before TB diagnosis or having other symptoms that lasted longer than 14 days and self-assessed these symptoms as being severe

[d]Aspartate aminotransferase ≥120 mEq/l, alanine aminotransferase ≥165 mEq/l, or total bilirubin >2 mg/dl

Table 3
Multivariate logistic regression analyses of risk factors for multi-drug resistant TB among pulmonary TB patients age ≥18 years old in the Thailand TB active surveillance network, Thailand (2004-2006).

	All TB patients		New TB patients	
	Excluding patients missing MDR-TB status(*n*=3,235)	Assuming patients missing MDR-TB status do not have MDR-TB (*n*=10,428)	Excluding patients missing MDR-TB status (*n*=2,614)	Assuming patients missing MDR-TB status do not have MDR-TB (*n*=7,968)
	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)
HIV status				
Infected	1.1(0.7-1.8)	1.06(0.7-1.6)	1.7(0.9-3.2)	1.5(0.8-2.9)
Uninfected	Ref	Ref	Ref	Ref
Unknown	1.5(0.8-2.8)	0.6(0.3-1.0)	2.1(0.9-4.8)	0.7(0.3-1.6)
Age (years)				
18-29	2.0(1.0-4.0)	1.8(0.9-3.4)	2.4(0.9-6.1)	1.0(0.3-3.2)
30-39	1.5(0.7-2.9)	1.7(0.9-3.2)	1.3(0.5-3.7)	1.8(0.7-4.6)
40-49	1.4(0.7-2.7)	1.6(0.9-3.0)	1.5(0.6-4.2)	1.7(0.6-4.5)
50-59	1.7(0.9-3.6)	2.6(1.4-4.9)	1.0(0.3-3.4)	3.4(1.3-8.8)
≥60	Ref	Ref	Ref	Ref
Sex				
Male	1.6(1.0-2.5)	1.6(1.1-2.4)	-	-
Female	Ref	Ref	-	-
Live in a crowded household[a]				
Yes	1.0(0.7-1.5)	0.9(0.6-1.2)	-	-
No	Ref	Ref	-	-
History of injection drug use				
Yes	1.5(0.8-3.0)	2.0(1.0-3.7)	3.1(1.3-7.3)	3.9(1.6-9.4)
No	Ref	Ref	Ref	Ref
Unknown	1.5(0.3-8.4)	1.9(1.0-3.5)	4.2(0.7-23.8)	3.1(1.2-8.2)
Live in a migrant or refugee camp				
Yes	0.4(0.1-1.8)	-	0.6(0.1-4.4)	-
No	Ref	-	Ref	-
Unknown	1.5(0.3-8.4)	-	2.1(0.3-12.8)	-
Type of registration				
New case	Ref	Ref	-	-
Relapse	6.3(3.7-10.8)	8.3(4.9-13.8)	-	-
Failure	42.9(22.7-81.2)	35.3(20.6-60.4)	-	-
Treatment after default	4.3(2.3-7.8)	5.4(3.0-9.7)	-	-
Transferred in	3.2(1.5-6.7)	2.4(1.2-4.9)	-	-
Other status	8.3(4.5-15.4)	4.6(2.6-8.1)	-	-
Single				
Yes	0.9(0.5-1.3)	-	0.9(0.5-1.9)	1.0(0.6-1.9)
No	Ref	-	Ref	Ref
Unknown	1.1 (0.3-4.1)	-	-	0.4(0.05-3.7)

Table 3 (Continued).

	All TB patients		New TB patients	
	Excluding patients missing MDR-TB status(*n*=3,235)	Assuming patients missing MDR-TB status do not have MDR-TB (*n*=10,428)	Excluding patients missing MDR-TB status (*n*=2,614)	Assuming patients missing MDR-TB status do not have MDR-TB (*n*=7,968)
	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)
Mobile				
Yes	-	Ref	Ref	Ref
No	-	1.3(0.8-1.9)	3.8(1.8-8.2)	3.2(1.5-6.9)
Unknown	-	0.1(0.01-0.5)	-	-
Abnormal chest radiography				
Yes	2.7(0.6-12.2)	-	4.0(0.9-18.8)	3.8(1.1-13.1)
No	Ref	-	Ref	Ref
Unknown	-	-	-	1.0 (0.4-2.5)
Thai nationality				
Yes	-	-	-	-
No	-	-	-	-
Live in municipal area				
Yes	1.0(0.7-1.5)	1.3(0.9-1.9)	1.4(0.7-2.6)	1.4(0.8-2.5)
No	Ref	Ref	Ref	Ref
Unknown	1.8 (0.6-5.3)	2.5(1.0-6.2)	-	0.9(0.1-6.7)
Previously diagnosed with diabetes				
Yes	-	-	2.4(0.9-6.7)	2.8(1.1-7.4)
No	-	-	Ref	Ref
Unknown	-	-	0.5(0.2-1.4)	0.4(0.2-1.1)

TB, tuberculosis; HIV; human immunodeficiency virus; AOR, adjusted odds ratio; CI, confidence interval; Ref, reference group

[a]Total individuals living in the same house ≥4

was diagnosed in 145, which was 1% of the patients in the surveillance study and 4% of patients in whom the DST was performed. In the surveillance study, 36% (52/145) of MDR-TB cases were HIV-infected, and 2% (52/2,376) of HIV-infected TB patients had MDR-TB.

In the observational study, DST was performed in 233 (43%) patients. MDR-TB was diagnosed in 19, which was 4% of all patients and 8% of patients in whom the DST was performed.

Risk factors for MDR-TB

Surveillance. Excluding patients with unknown MDR-TB status, independent risk factors for MDR-TB were age 18-29 years old [adjusted odds ratio (AOR) 2.0; 95% confidence interval (95% CI), 1.0-4.0] and being male (AOR 1.6; 95% CI 1.0-2.5) (Table 3). Previous TB treatment was strongly associated with MDR-TB. Compared to new TB patients, patients who previously failed TB treatment were the most likely to have MDR-TB (AOR 42.9; 95% CI 22.7-81.2), followed

Table 4
Multivariate analyses of risk factors for multi-drug resistant TB among HIV-infected pulmonary TB patients age ≥18 years old and enrolled in the observational study, Thailand (2004-2006).

	All TB patients		New TB patients	
	Excluding patients missing MDR-TB status(*n*=201)	Assuming patients missing MDR-TB status do not have MDR-TB (*n*=478)[a]	Excluding patients missing MDR-TB status (*n*=194)	Assuming patients missing MDR-TB status do not have MDR-TB (*n*=442)
	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)
Age (years)				
18-29	5.3(0.7-39.1)	4.5(0.7-29.2)	3.8(0.6-23.0)	2.4(0.4-13.9)
30-39	1.9(0.3-13.5)	2.6(0.5-14.6)	1.4(0.2-8.8)	1.2(0.2-6.9)
≥40	Ref	Ref	Ref	Ref
Sex				
Male	1.0(0.2-4.3)	1.0(0.3-3.9)	0.8(0.2-3.6)	0.8(0.2-3.2)
Female	Ref	Ref	Ref	Ref
Diagnosed with HIV >30 days before TB diagnosis				
Yes	1.2(0.3-4.5)	1.5(0.4-5.1)	-	-
No	Ref	Ref	-	-
Previously diagnosed with hepatitis				
Yes	10.8(1.6-73.9)	10.4(2.1-51.6)	-	-
No	Ref	Ref	-	-
History of methamphetamine use				
Yes	2.0(0.5-8.7)	1.9(0.5-7.3)	-	-
No	Ref	Ref	-	-
History of injection drug use				
Yes	1.4(0.2-8.8)	0.9(0.2-4.2)	-	-
No	Ref	Ref	-	-
History of incarceration				
Yes	1.1(0.2-5.4)	1.2(0.3-5.0)	-	-
No	Ref	Ref	-	-
History of alcohol use				
Yes	2.2(0.5-10.9)	-	4.9(0.6-41.7)	4.1(0.5-34.3)
No	Ref	-	Ref	Ref
Reactive for hepatitis B antigen				
Yes	1.5(0.3-7.9)	1.4(0.3-6.3)	-	-
No	Ref	Ref	-	-
Reactive for anti-hepatitis C antibody				
Yes	1.1(0.2-6.8)	-	-	-
No	Ref	-	-	-
Abnormal liver enzyme level[b]				
Yes	1.0(0.3-4.3)	2.0(0.6-7.0)	1.8(0.5-7.2)	3.0(0.8-11.4)
No	Ref	Ref	Ref	Ref

Table 4 (Continued).

	All TB patients		New TB patients	
	Excluding patients missing MDR-TB status(*n*=201)	Assuming patients missing MDR-TB status do not have MDR-TB (*n*=478)[a]	Excluding patients missing MDR-TB status (*n*=194)	Assuming patients missing MDR-TB status do not have MDR-TB (*n*=442)
	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)
Abnormal hemoglobin level				
Yes	-	-	-	1.1(0.3-4.3)
No	-	-	-	Ref
Registered as a new case				
Yes	Ref	Ref	-	-
No	5.0(1.4-25.0)	5.0(1.4-10.0)	-	-
CD4+ T-lymphocyte level at enrollment	1.0(1.0-1.0)	1.0(1.0-1.0)	1.0(1.0-1.0)	1.0(1.0-1.0)
Hospitalized at enrollment				
Yes	-	-	-	2.0(0.5-7.6)
No	-	-	-	Ref
Delay in TB diagnosis[c]				
Yes	-	-	0.4(0.1-1.4)	0.5(0.1-1.7)
No	-	-	Ref	Ref

TB, tuberculosis; human immunodeficiency virus; AOR, adjusted odds ratio; CI, confidence interval; MDR-TB, multi-drug resistant tuberculosis; Ref, reference

[a]61 patients with missing data for one or more model terms were dropped from the final model

[b]Aspartate aminotransferase ≥120 mEq/l, alanine aminotransferase ≥165 mEq/l, or total bilirubin >2 mg/dl

[c]Reported having a cough lasting greater than one month before TB diagnosis or had severe symptoms lasting longer than 14 days and greater than self-assessed intensity score of five

by patients who were registered as "other" (AOR 8.3; 95% CI 4.5-15.4), as relapse (AOR 6.3; CI 3.7-10.8), as treatment after default (AOR 4.3; 95% CI 2.3-7.8), and as transferred in (AOR 3.2; 95% CI 1.5-6.7). When we assumed patients with missing MDR-TB status did not have MDR-TB, being male and having previously been treated for TB remained risk factors. We found MDR-TB was associated with age 50-59 years (AOR 2.6; 95% CI 1.4-4.9) and a history of injection drug use (AOR 2.0; 95% CI 1.0-3.7). When we analyzed an imputed dataset, the only factors associated with MDR-TB were being male sex (AOR 1.4; 95% CI 1.0-2.0), being age 18-29 years old (AOR 1.9; 95% CI 1.1-3.1), and having previously been treated for TB (registered as relapse: AOR 4.8; 95% CI 2.7-8.4; registered as failure: AOR 17.4; 95% CI 9.9-30.7; registered as treatment after default: AOR 4.4; 95% CI 2.4-8.1; registered as transferred in case: AOR 3.0; 95% CI 1.5-5.8; registered as "other" and not new case: AOR 5.7; 95% CI 3.6-8.9).

In the subset of new TB patients, risk factors for MDR-TB were having a history

of injection drug use (AOR 3.1; 95% CI 1.3-7.3) and not being mobile (AOR 3.8; 95% CI 1.8-8.2). When we assumed that patients with missing MDR-TB status did not have MDR-TB, these two factors remained independently associated with MDR-TB; additional risk factors identified included age 50-59 years old (AOR 3.4; 95% CI 1.3-8.8). unknown history of injection drug use (AOR 3.1; 95% CI 1.2-8.2), abnormal chest radiograph (AOR 3.8; 95% CI 1.1-13.1), and previous diabetes diagnosis (AOR 2.8; 95% CI 1.1-7.4). When we analyzed an imputed dataset, injection drug use (AOR 2.1; 95% CI 1.0-4.4) and not being mobile (AOR 1.9; 95% CI 1.2-3.0) were the only factors associated with MDR-TB.

Observational study. Among HIV-infected TB patients, the only significant risk factors were: previous TB treatment (AOR 5.0; 95% CI 1.4-10.0, assuming the patients missing MDR-TB status did not have MDR-TB; AOR 5.0; 95% CI 1.4-25.0 excluding the patients missing MDR-TB status) and a previous diagnosis of hepatitis (AOR 10.4; 95% CI 2.1-51.6, assuming the patients missing MDR-TB status did not have MDR-TB; AOR 10.8, 95% CI 1.6-73.9, excluding the patients missing MDR-TB status) (Table 4). Of 18 patients with a history of hepatitis, 5 (28%) were reactive to hepatitis B surface antigen (HBsAg) and 8 (44%) to hepatitis C virus (anti-HCV); 4 (22%) were both HBsAg and anti-HCV reactive. Of those with a history of hepatitis, 4 (22%) had abnormal liver function tests at baseline.

DISCUSSION

In Thailand, we found HIV infection was common among MDR-TB patients, but was not an independent risk factor for MDR-TB. Among HIV-infected patients, the only factors associated with MDR-TB were a previous history of TB treatment and of hepatitis.

We conducted multiple statistical analyses to account for previous TB treatment, HIV status, and missing MDR-TB data. In doing so, we found that some characteristics were associated with MDR-TB on one analysis, but not on other analyses. Nevertheless, some consistent findings emerged. HIV was not an independent risk factor for MDR-TB in any analysis, but populations at high risk for HIV infection were more likely to have MDR-TB, including young men (on analysis of all cases) and injection drug users (on analysis of new TB cases). We suspect being a young man may be a surrogate marker for either injection drug use or an incarceration history. Our measurement of drug use was based on either patient self-reporting or physician diagnosis, both of which are likely to be insensitive, and we did not collect data about incarceration history in our surveillance system. In Thailand, most injection drug users are men, and HIV infection and incarceration occur frequently (Kitayaporn *et al*, 1998; Wattana *et al*, 2007). One previous study at a referral hospital in Bangkok and another conducted among prisons found a close overlap between men, drug use, prison, HIV infection, and MDR-TB (Punnotaok *et al*, 2000; WHO, 2003). Combining our study's findings with these previously published data, we believe that culture and DST should be performed in any patient with a history of injection drug use, incarceration, or HIV infection in Thailand, regardless of previous TB treatment history.

Our findings also indicate that culture and DST should be performed on any patient with a history of previous TB treatment, regardless of whether they defaulted from, relapsed after, or failed previous treatment. Among those that failed, the odds of MDR-TB were particularly high. Given the known problem of amplification of drug-resistance, consideration should be given to providing

empiric MDR-TB treatment to all patients with a history of failure, rather than using the Category II "re-treatment" regimen (WHO, 2003, 2006). One curious finding was the association between MDR-TB and persons who were not mobile, which was defined as those who had lived in the same district for at least three of the past six months. Since program experience in Thailand is actually the reverse–that mobile populations are less adherent to TB treatment and, therefore, at risk for MDR-TB–it is possible that this variable was a marker for some other unmeasured factors, such as better access to TB diagnostic services among non-mobile populations.

Among HIV-infected TB patients, we found that previous treatment and a history of hepatitis were the only risk factors for MDR-TB. We could not identify any factors predictive of MDR-TB among new TB patients. Hepatitis is a known complication of anti-TB therapy, particularly with MDR-TB, but it has not previously been documented to be a risk factor for acquisition of drug resistance (Törün *et al*, 2005). Our definition of hepatitis included any patient self-report or medical record documentation of previous clinical hepatitis, regardless of etiology. Further studies evaluating the association between MDR-TB and HIV should include assessments of pre-existing liver disease.

A major limitation of our study is that HIV testing and DST were not provided to all patients. In our project sites, we have established facilities to do routine culture and DST for all TB patients, but obtaining DST for all patients is challenging in high-burden, resource-limited settings. Physicians who are trained to rely on smear microscopy do not routinely order sputum cultures; specimens, if received, in the laboratory may be inadequate for culture; cultures may not grow or become contaminated, particularly with smear-negative specimens; and DST may not be possible because of inadequate growth on culture (McCarthy *et al*, 2008). Because HIV-infected patients frequently have paucibacillary or extra-pulmonary TB, it is possible that they were systematically less likely to have positive mycobacterial cultures, reducing the likelihood of having isolates available for DST (Burman, 2005). The cohort of HIV-infected patients had a lower proportion of patients that were previously treated for TB compared with those in surveillance, but we do not know how inclusion of these patients would have impacted our findings. Nevertheless, we believe that we would have found an association between HIV and MDR-TB in Thailand if one truly existed. A major strength of our study is that it was conducted prospectively within the routine public health system in Thailand and included a diverse mix of large and small, urban and rural health facilities in several geographic regions. We analyzed a large number of cases, HIV testing rates were relatively high, and we used multiple statistical methods to account for missing data. Use of multiple imputation, in particular, has been shown to produce valid statistical estimates when analyzing data with missing values (Donders *et al*, 2006).

In conclusion, we found that HIV was not an independent risk factor for MDR-TB in Thailand, but populations at high risk for HIV–young men with a history of injection drug use–are the highest risk group for MDR-TB. Combating this problem will require focusing on this group but, even more importantly, will require renewed investments in basic TB control, expanded access to modern TB diagnostics and therapeutics, strict infection control practices in hospitals and prisons, and ongoing surveillance to monitor trends and evolving risk factors.

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