Original Article

Human Immunodeficiency Virus Infection-Associated Mortality during Pulmonary Tuberculosis Treatment in Six Provinces of China*

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Abstract

Objective To investigate the risk factors attributable to tuberculosis-related deaths in areas with human immunodeficiency virus (HIV) infection epidemics.

Methods A prospective cohort study of newly registered patients in tuberculosis (TB) dispensaries in six representative Chinese provinces was conducted from September 1, 2009 to August 31, 2011. Risk factors for TB-associated death were identified through logistic regression analysis.

Results Of 19,103 newly registered pulmonary TB patients, 925 (4.8%) were found to be HIV-positive. Miliary TB and acid-fast bacillus smear-negative TB were more common among these patients. Out of a total of 322 (1.7%) deaths that occurred during TB treatment, 85 (26%) of the patients were co-infected with HIV. Multivariate analysis revealed that HIV infection was the strongest predictor of death [adjusted odds ratio (aOR) 7.86]. Other significant mortality risk factors included presentation with miliary TB (aOR 4.10; 95% confidence interval: 2.14-7.88), ≥35 years of age (aOR 3.04), non-Han ethnicity (aOR 1.67), and farming as an occupation (aOR 1.59). For patients with TB/HIV co-infection, miliary TB was the strongest risk factor for death (aOR 5.48). A low CD4 count (≤ 200 cells/μL) (aOR 3.27) at the time of TB treatment initiation and a lack of antiretroviral therapy (ART) administration (aOR 3.78) were also correlated with an increased risk of death.

Conclusion Infection with HIV was independently associated with increased mortality during TB treatment. Offering HIV testing at the time of diagnosis with TB, early TB diagnosis among HIV/acquired immunodeficiency syndrome patients, and the timely provision of ART were identified as the key approaches that could reduce the number of HIV-associated TB deaths.

Key words: Tuberculosis; Human immunodeficiency virus; Acquired immunodeficiency syndrome; Mortality

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INTRODUCTION

Tuberculosis (TB) and human immunodeficiency virus (HIV) infection are a devastating combination. The most common opportunistic infection is TB, which is a leading cause of death among individuals living with HIV/AIDS, especially in developing counties[1]. Globally, 13% of all reported TB patients in 2011 were co-infected with HIV, and 79% of these patients lived in Africa[2]. Similarly, HIV infection is known to increase TB patient mortality due to rapid disease dissemination as a result of an impaired immune system. Therefore, HIV positive patients tend to present with an atypical form of TB, which can delay accurate diagnosis and treatment and thus can result in premature death[3-4].

Because the majority of TB/HIV co-infection studies have been conducted in African countries that have a high prevalence of both HIV infection and TB, there is a lack of information on other countries such as China where the TB incidence is high but the prevalence of HIV infection is low. Despite the low HIV infection prevalence (0.06%)[5], China has an immense population that accounts for the large number of total absolute infections, with more than 70% of all HIV/acquired immunodeficiency syndrome (AIDS) cases coming from rural areas[6]. Similarly, the number of TB cases in China is almost two-fold higher in rural settings[7]. Additionally, China has a serious epidemic of drug-resistant tuberculosis[8]. Along with the increasing HIV prevalence in China, especially among high-risk populations, the risk of co-infection with TB or multidrug-resistant TB also increases and, consequently, there are significant public health implications[9].

In order to address this issue, the National TB Program (NTP) in China conducted a project that targeted TB/HIV co-infection in 2007 in a partnership with the Global Fund to Fight AIDS, Tuberculosis and Malaria. We aimed to explore the impact of HIV infection on the mortality of TB patients and analyze the associated risk factors that can be attributed to these deaths within the project area.

MATERIALS AND METHODS

Study Population

This retrospective cohort analysis investigated the effect of HIV infection on pulmonary TB mortality for patients who received the standard of care for TB therapy in six provinces that comprised 14 counties in China between September 1, 2009 and August 31, 2011. The regions selected for data analysis had TB and HIV incidences that were higher than the national average for China and had known high-risk HIV transmission routes, which included (1) having a history of illegal, pooled plasma donations in the early 1990s (Henan, Anhui, and Hubei provinces, which included the nine counties of Suixian, Shangcai, Xincai, Jiesou, Funan, Xiaoxian, Daye, Nanzhang, and Jingchun), or (2) having a high prevalence of injection drug use and sexually transmitted infections (the Guangxi, Xinjiang, and Sichuan provinces, which included the five counties of Hengxian, Luzai, Kuche, Yining, and Dazhu).

All newly diagnosed and registered active pulmonary TB patients who had completed HIV testing in the study areas during the time period were included. We excluded patients who did not receive TB treatment during the study period because of either missing or incomplete treatment or records. Additionally, patients without a confirmatory acid-fast bacilli (AFB) sputum result, chest X-ray radiography (CXR), or other pathological confirmation of a TB diagnosis were excluded from the study. Extra-pulmonary TB patients (EPTB) were excluded due to the requirement for long-term therapy. During the two-year study period, there were 19,103 patients who were included in the final analysis.

Procedures and Definitions

All newly registered active TB patients in the selected counties underwent HIV antibody testing through a provider-initiated HIV testing and counseling approach. Standardized two-step HIV testing was performed using: (1) HIV antibody screening with the enzyme-linked immunosorbent assay (ELISA) and (2) confirmatory Western blot testing[10]. Name-based Western blot testing was performed as a confirmation for patients who had two different positive ELISA tests, based on the national guidelines for the detection of HIV/AIDS (2009) of China[10].

Previously confirmed HIV-positive patients, who were referred from the local HIV clinical system because of suspected TB symptoms had no need for repeat HIV testing as defined by Chinese national guidelines[11] and were offered TB diagnostic and treatment services at local TB clinics.

Active pulmonary TB was diagnosed based on

sputum smear examinations for AFB and CXR for any patient suspected to have TB at local TB dispensaries (clinics). The source of potential TB patients included individuals who presented with TB symptoms and either actively sought care or who were referred by other health institutes including local HIV programs. Once diagnosed with active TB, patients were reported and recorded in the local TB registry, which is also part of the Chinese national TB control and prevention program of China. All registered TB patients received the standard anti-TB medication free of charge according to the Chinese national TB guidelines, which is consistent with the World Health Organization (WHO) recommendations[12]. After TB treatment initiation, the patients were followed by local TB dispensaries for either 6 months (new TB patients) or 8 months (retreated TB patients)[11]. For TB/HIV co-infected patients, the anti-TB medication regimen was administered first. Once it was tolerated, antiretroviral therapy (ART) was administered in the HIV clinics. For patients who were already receiving ART, TB treatment was initiated immediately after diagnosis, and the ART regimen was adjusted accordingly such as by substituting nevirapine with efavirenz.

The information regarding patients in the local TB registry included basic demographic characteristics, the source of the referral (either self-referral or second party referral), the TB category (miliary *vs.* cavitary), radiological examination results, anti-TB treatment details, and the treatment outcome (such as treatment completion, treatment failure, relapse, default, or death). Patients with HIV/TB co-infection were defined as either TB patients confirmed with HIV infection or confirmed HIV patients with an active TB diagnosis. Additional data were collected for TB/HIV co-infected patients regarding the potential route of HIV transmission, whether they received ART during anti-TB treatment, and the CD4 cell count at the time TB treatment was initiated. The data for HIV-positive patients were kept confident through the use of a de-identified patient identification marker.

Ethical Approval

Ethical approval for the use of routine patient data regarding TB and HIV co-infection in the TB reporting system was obtained from the Ethical Review Committee of the Chinese Center for Disease Control and Prevention.

Statistical Analysis

The data were securely extracted from the NTP database and analyzed statistically using SPSS (Version 13.0, SPSS Inc., Chicago, IL, USA). The primary outcome was all-cause mortality during the pulmonary TB treatment period and was defined as the number of deaths divided by the total number of patients on anti-TB treatment. To investigate whether the overall mortality during TB treatment differed by HIV infection status, we performed step-wise univariate and multivariate logistic regression analysis with 95% confidence intervals (CIs), in the absence of information regarding the time of death for each patient in the database. Correlates with the odds ratios (ORs), which were significant at a *P*-value <0.05 at the univariate level, were incorporated into the multivariate model using a forward selection approach, thus adjusting for factors such as sociodemographic variables (gender, age, and occupation) and the TB categories. Univariate analysis was then performed for TB/HIV co-infected patients only. A multivariate model was generated that included all variables considered to be high-risk for mortality, regardless of *P*-value.

RESULTS

Of the 19,103 total active TB cases included in the final analysis, 925 (4.8%) were HIV-positive, of which 673 (72.8%) were referred from the HIV clinics with symptoms suggestive of TB. Of the sample 252 (27.2%) were newly diagnosed as HIV-positive at the TB dispensaries. The median age of the study population was 47.7±19.2 years. Most of the patients were male (71.2%), of Han ethnicity (89.1%), and were agricultural workers (farmers) (80.1%). There were 322 deaths, which resulted in a 1.7% mortality during anti-TB treatment of all diagnosed active pulmonary TB patients. Of these patients, 85 (26%) were also co-infected with HIV.

When the HIV-positive and negative population groups were compared, patients with HIV infection were generally younger than those without infection (median age 38 *vs.* 50 years) (Table 1). There were fewer agricultural workers in the HIV-positive group than in the HIV-negative group [589 (63.7%) *vs.* 14,717 (81%), *P*<0.001], and there were nearly four-fold more minorities in the HIV-positive group compared to the HIV-negative group [322 (34.8%) *vs.* 1756 (9.7%), *P*<0.001]. The AFB sputum positivity rates among the HIV-positive subjects were lower

than those of the HIV-negative subjects [251/925 (27.1%) *vs.* 10,741/18,178 (59.1%), *P*<0.001). Cavitary TB was less frequently observed on CXRs of HIV-positive patients compared to those of HIV-negative TB patients [52/925 (5.6%) *vs.* 2162/18,178 (11.9%), *P*<0.001]. A higher proportion of miliary TB was observed among HIV-positive TB patients compared to HIV-negative TB patients [20/925 (2.2%) *vs.* 180/18,178 (1.0%), *P*=0.002].

We identified risk factors for TB-associated death using logistic regression analysis. In the univariate analysis (Table 2), the results showed that HIV infection was highly associated with increased mortality among TB patients who received anti-TB treatment (OR 7.66, 95% CI 5.92-9.91; *P*<0.001). The second most significant risk factor was severe TB disease presenting with miliary TB on CXR (OR 3.48, 95% CI 1.88-6.46; *P*<0.001). Other factors such as age ≥35 years (OR 2.94, 95% CI 2.11-4.10; *P*<0.001), farming as an occupation (OR 1.42, 95% CI 1.05-1.94; *P*=0.025), and non-Han ethnicity (OR 1.82, 95% CI 1.37-2.43; *P*<0.001) were also associated with an increased risk of death during anti-TB treatment. Gender, sputum smear positivity, and cavitary lesions on CXR were not associated with increased mortality. Multivariate analysis revealed that the effects of HIV infection remained the strongest predictor of death (aOR 7.86, 95% CI 5.95-10.40; *P*<0.001) (Table 2). Miliary TB was the second highest risk factor for death (aOR 4.10, 95% CI 2.14-7.88; *P*<0.001) followed by age ≥35 years old, which resulted in a three-fold increase in mortality (aOR 3.04, 95% CI 2.14-4.32; *P*<0.001). Additionally, non-Han ethnicity (aOR 1.67, 95% CI 1.20-2.31; *P*=0.002) and farming as an occupation (aOR 1.59 95% CI 1.11-2.26; *P*=0.011) were also significantly associated with increased death after adjustment for other risk factors.

Table 1. Baseline Demographics of Selected Pulmonary Tuberculosis Patients by Human Immunodeficiency Virus Infection Status in China between 2009 and 2011, *N*=19,103

Characteristics	HIV-positive (Total=925) *n* (%)	HIV-negative (Total=18,178) *n* (%)	*P*-value
Gender			
Male	693 (74.9)	12,914 (71.0)	0.012
Female	232 (25.1)	5,264 (29.0)	
Age (y)			
Mean (Std)	39.7±11.2	48.1±19.4	<0.001
Ethnicity			
Han	603 (65.2)	16,422 (90.3)	<0.001
Minorities	322 (34.8)	1,756 (9.7)	
Occupation			
Farmer	589 (63.7)	14,717 (81.0)	<0.001
Other	336 (36.3)	3,461 (19.0)	
Sputum results			
Positive	251 (27.1)	10,741 (59.1)	<0.001
Negative	674 (72.9)	7,437 (40.9)	
Cavitary TB on CXR^+			
Yes	52 (5.6)	2,162 (11.9)	<0.001
No	873 (94.4)	16,016 (88.1)	
Miliary TB on CXR^+			
Yes	20 (2.2)	180 (1.0)	0.002
No	905 (97.8)	17,998 (99.0)	

Note. CXR=Chest X-ray radiography; HIV= Human immunodeficiency virus; Std=standard deviation; TB=Tuberculosis.

We also investigated risk factors for TB/HIV-related death during TB treatment using univariate and multivariate logistic regression analysis (Table 3). Before adjusting for other risk factors, a lower CD4 count (≤200 cells/μL) was associated with the highest risk of death (OR 3.53, 95% CI 1.68-7.45; *P*=0.001). The factors that were associated with an increased risk death in the univariate analysis included not receiving ART during TB treatment (OR 2.22, 95% CI 1.40-3.51; *P*=0.001), not receiving cotrimoxazole prophylaxis during the TB treatment period (OR 1.59, 95% CI 1.01-2.50; *P*=0.044), and identification of new patients with HIV infection at TB dispensaries rather than referral from an HIV clinic (OR 1.80, 95% CI 1.13-2.86; *P*=0.013). However, after adjusting for other risk factors, miliary presentation on CXR showed the strongest association, with a >5-fold increased risk of death among TB/HIV co-infected patients during the TB treatment period (aOR 5.48, 95% CI 1.30-23.18; *P*=0.021). Not receiving ART during TB treatment was the next strongest risk factor for TB/HIV-related death (aOR 3.78, 95% CI: 1.64-8.71; *P*=0.002). A low baseline CD4 count (≤200 cells/μL) at the time of TB treatment initiation was also correlated with increased death among TB/HIV patients during the TB treatment period (aOR 3.27, 95% CI 1.46-7.31; *P*=0.004). The risk of newly diagnosed HIV at TB dispensaries and the protective effect of cotrimoxazole prophylaxis therapy against death among TB/HIV patients were statistically significant, but the effects of these factors vanished after adjustment for other risk factors.

DISCUSSION

We found that there was a nearly eight-fold increase in deaths among HIV-positive compared to HIV-negative TB patients. This is the first study to use national data to quantify the effect of HIV infection on TB-related mortality in China. One possible concern is that HIV-associated TB may not be a priority for TB control programs in countries such as China, where the TB incidence is high but the HIV prevalence is low. However, our study illustrates that although the overall mortality among TB patients during the anti-TB treatment period was low (1.7%), nearly a third (26%) of these deaths were associated with HIV infection. These results are consistent with other studies in the literature, which have posited that HIV-positive patients had a higher risk of death than HIV-negative patients[3,13-14]. To meet the target for the Millennium Development Goal 6, which is to reduce the prevalence and numbers of deaths due to TB by 50%, China, which has a large population and high incidence of TB, can contribute to global efforts by focusing on HIV-associated TB control and prevention.

Miliary TB, which is also called disseminated TB, is associated with a mortality of approximately 25%-30%. This disease is more frequently encountered among immunosuppressed individuals[15]. Similarly, in our study, miliary TB was more likely to be observed in HIV-infected TB patients and led to a four-fold higher mortality than that of HIV-negative TB patients. Presentation of miliary TB often indicates that the patient has a very weak immune system that is unable to control the dissemination of the disease, and leads to a higher risk of mortality despite treatment with effective therapy[16].

Table 2. Risk Factors Associated with Mortality in Patients Infected with Pulmonary Tuberculosis in China between 2009 and 2011, *N*=19,103

Characteristics	Patients Received TB Treatment (Total=19,103)	Deaths (Total=322)	Unadjusted OR (95% CI; *P*-value)	Adjusted OR (95% CI; *P*-value)
Gender				
Male	13,607 (71.2%)	245/13,607 (1.8%)	Reference	-
Female	5,496 (28.8%)	77/5,496 (1.4%)	0.78 (0.60-1.00; *P*=0.053)	-
Age (y)				
<35	5,570 (29.2%)	40/5,570 (0.7%)	Reference	Reference
≥35	13,533 (70.8%)	282/13,533 (2.1%)	2.94 (2.11-4.10; *P*<0.001)	3.04 (2.14-4.32; *P*<0.001)
Ethnicity				
Han	17,025 (89.1%)	264/17,025 (1.6%)	Reference	Reference
Minority	2,078 (10.9%)	58/2,078 (2.8%)	1.82 (1.37-2.43; *P*<0.001)	1.67 (1.20-2.31; *P*=0.002)
Occupation				
Other	3,797 (19.9%)	48/3,797 (1.3%)	Reference	Reference
Agricultural Worker	15,306 (80.1%)	274/15,306 (1.8%)	1.42 (1.05-1.94; *P*=0.025)	1.59 (1.11-2.26; *P*=0.011)
Sputum results				
Positive	10,992 (57.5%)	169/10,992 (1.5%)	Reference	-
Negative	8,111 (42.5%)	153/8,111 (1.9%)	1.11 (0.99-1.24; *P*=0.065)	-
Cavitation on CXR$^+$				
No	16,889 (88.4%)	283/16,889 (1.7%)	Reference	-
Yes	2,214 (11.6%)	39/2,214 (1.8%)	1.05 (0.75-1.48; *P*=0.768)	-
Miliary TB on CXR$^+$				
No	18,903 (99.0%)	311/18,903 (1.6%)	Reference	Reference
Yes	200 (1.0%)	11/200 (5.5%)	3.48 (1.88-6.46; *P*<0.001)	4.10 (2.14-7.88; *P*<0.001)
HIV infection status				
Negative	18,178 (95.2%)	237/18,178 (1.3%)	Reference	Reference
Positive	925 (4.8%)	85/925 (9.2%)	7.66 (5.92-9.91; *P*<0.001)	7.86 (5.95-10.40; *P*<0.001)

Note. CI=Confidence interval; CXR=Chest X-ray radiography; HIV=Human immunodeficiency virus; OR=Odds ratio; TB=Tuberculosis.

Table 3. Risk Factors for Mortality among Patients Co-infected with Tuberculosis/Human Immunodeficiency Virus Who Received Anti-tuberculosis Treatment

Characteristics	TB/HIV Patients on TB treatment (Total=925)	Deaths (Total=85)	Unadjusted OR (95% CI; *P*-value)	Adjusted OR (95% CI; *P*-value)
Gender				
Male	693 (74.9%)	61/693 (8.8%)	Reference	Reference
Female	232 (25.1%)	24/232 (10.3%)	1.20 (0.73-1.97; *P*=0.482)	1.10 (0.50-2.39; *P*=0.816)
Age (y)				
<35	290 (31.4%)	19/290 (6.6%)	Reference	Reference
≥35	635 (68.6%)	66/635 (10.4%)	1.65 (0.97-2.81; *P*=0.063)	2.13 (0.90-5.05; *P*=0.087)
Ethnicity				
Han	603 (65.2%)	55/603 (9.1%)	Reference	Reference
Minorities	322 (34.8%)	30/322 (9.3%)	1.02 (0.64-1.63; *P*=0.922)	0.56 (0.20-1.62; *P*=0.287)
Occupation				
Other	336 (36.3%)	27/336 (8.0%)	Reference	Reference
Farmer	589 (63.7%)	58/589 (9.8%)	1.25 (0.78-2.02; *P*=0.360)	1.02 (0.36-2.89; *P*=0.971)
Sputum results				
Positive	251 (27.1%)	26/251(10.4%)	Reference	Reference
Negative	674 (72.9%)	59/674 (8.8%)	0.91 (0.72-1.16; *P*=0.453)	1.06 (0.74-1.51; *P*=0.768)
Cavitary TB on the CXR$^+$				
No	873 (94.4%)	78/873 (8.9%)	Reference	Reference
Yes	52 (5.6%)	7/52 (13.5%)	1.59 (0.69-3.64; *p*= 0.276)	1.91 (0.51-7.09; *P*=0.334)
Miliary TB on CXR$^+$				
No	887 (97.8%)	80/887 (9.0%)	Reference	Reference
Yes	20 (2.2%)	4/20 (20.0%)	2.54 (0.83-7.79; *P*=0.102)	5.48 (1.30-23.18; *P*=0.021)
Patients source				
Referred from HIV clinic	673 (72.8%)	52/673 (7.7%)	Reference	Reference
New HIV diagnosed at TB dispensary	252 (27.2%)	33/252 (13.1%)	1.80 (1.13-2.86; *P*=0.013)	1.35 (0.65-2.81; *P*=0.426)
Transmission route				
Injection drug use	189 (20.4%)	14/189 (7.4%)	Reference	Reference
Sexual transmission	157 (17.0%)	15/157 (9.6%)	1.32 (0.62-2.83; *P*=0.474)	0.58 (0.19-1.79; *P*=0.338)
Former plasma donation	368 (39.8%)	32/368 (8.7%)	1.19 (0.62-2.29; *P*=0.601)	0.69 (0.22-2.19; *P*=0.524)
Other	211 (22.8%)	24/211 (11.4%)	1.60 (0.80-3.20; *P*=180)	0.55 (0.17-1.79; *P*=0.322)
CD4 count at TB treatment initiation				
>200 cells/μL	320 (45.2%)	9/320 (2.8%)	Reference	Reference
≤200 cells/μL	388 (54.8%)	36/388 (9.3%)	3.53 (1.68-7.45; *P*=0.001)	3.27 (1.46-7.31; *P*=0.004)
Received ART during TB treatment period				
Yes	513 (55.5%)	32/513 (6.2%)	Reference	Reference
No	412 (44.5%)	53/412 (12.9%)	2.22 (1.40-3.51; *P*=0.001)	3.78 (1.64-8.71; *P*=0.002)
Received CPT during TB treatment period				
Yes	614 (66.4%)	48/614 (7.8%)	Reference	Reference
No	311 (33.6%)	37/311 (11.9%)	1.59 (1.01-2.50; *P*=0.044)	0.42 (0.16-1.09; *P*=0.073)

Note. ART=Antiretroviral therapy; CI=Confidence interval; CPT=Cotrimoxazole prophylaxis therapy to patients with CD4 <200 cells/μL; CXR=Chest X-ray radiography; OR=Odds ratio; TB=Tuberculosis.

Treatment with ART can effectively reduce the mortality among TB/HIV co-infected patients[17-19]. In our study, a lack of ART administration was independently associated with an increased risk of death, and the protective effect of ART increased by 70% after controlling for other factors. A low baseline CD4 count (≤200 cells/μL) at the time of TB diagnosis was also significantly associated with a nearly four-fold higher risk of death[18-19]. Therefore, a better response in order to control TB/HIV co-infection requires comprehensive approaches including earlier HIV detection among TB patients, better diagnostic tools for TB disease, and timely administration of ART at any CD4 level (which is also recommended by the WHO)[12] to prevent progression of immune deficiencies that can lead to death in co-infected patients.

Other risk factors independent of HIV infection that contributed to the TB deaths found in our study included age ≥35 years, non-Han ethnicity, and farming as the primary occupation. Older individuals tend to be exposed to several co-morbidities due to weakening immune systems[20-21]. The high death rates among farmers and minorities could be explained by the current situations of Chinese migrant workers, who travel from rural and minority communities[6,21-22] and encounter limited access to health care services and social support in urban environments. A study by Abuaku et al. from Hunan, confirmed that migrant workers from rural areas had difficulty accessing TB treatment in new urban environments for a variety of reasons[23]. Therefore, the needs of these migrant workers should be prioritized in order to improve their health outcomes, particularly in relation to HIV and TB.

The HIV prevalence among newly diagnosed TB patients in this study was 4.8%. This figure was lower than the international average, especially compared to countries with high TB burdens. In 2011, the WHO reported that 13% of active TB patients worldwide were also HIV-positive. Infection with HIV has led to an increase in the number of TB cases due to an increased risk of transmission in vulnerable populations and reactivation of the TB infection resulting in active TB disease and increasing the course of TB[24]. In general, the HIV positivity rate among TB patients was approximately 40%-70% in South Africa[25] where the prevalence of HIV was also very high in the general population. In countries where HIV was not rampant, the HIV positivity rate among TB patients was approximately 8%-10%[25]. In China, TB prevalence is not highly associated with HIV prevalence. The HIV testing rate among all registered TB patients in our study was >98%, which could reflect the true HIV prevalence among the study population.

There were several limitations in this study. First, we selected areas with high HIV prevalence and high TB/HIV co-infection rates in order to explore the relationship between HIV and TB. However, the high levels may not have been representative of the country as a whole. Second, although there is evidence in the literature that EPTB occurs more frequently in HIV-positive patients than HIV-negative patients, we were unfortunately unable to include the EPTB data due to the long-term therapy involved and the incompleteness of the surveillance reporting system. Thus, the TB/HIV mortality rates reported here, though dramatic, could actually be higher than the values we reported. Thus, our data may underestimate the true disease burden. In addition, at the time of the study, the recommended treatment duration for military TB was 6 months, though in practice many physicians would treat for a longer duration based on disease burden. The 2015 TB guidelines in China will recommend a longer treatment course for military TB of up to one year.

In a conclusion, HIV infection contributed to an eight-fold increase in TB mortality in China, which represents a setting with high prevalence of TB and a low prevalence of HIV. Further interventions are needed to decrease the barriers to testing and treatment for HIV and TB among populations that are the most at risk for infection in China, specifically older aged migrant farm workers. Although ART can effectively reduce mortality among patients with TB/HIV co-infection, HIV infection was independently associated with increased mortality during TB treatment. Thus, offering HIV testing at the time of TB diagnosis, early TB diagnosis among HIV/AIDS patients, and the timely administration of ART have been identified as the key approaches for reducing HIV-associated TB deaths.

CONFLICTS OF INTEREST

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or in the writing of the report. The corresponding author had full access to all of the data in the study and was responsible for the decision to submit the manuscript for publication. The opinions expressed in this paper are those of the

authors and do not necessarily reflect the official position of the Chinese Center for Disease Control and Prevention. The authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

The following authors conceived and designed the experiments: SC, NW, LZ, and YL. The experiments were performed by YL, EL, and LZ. The data were analyzed by YL, EL, LW, JPM, and KK wrote the manuscript.

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