

## Tuberculosis and HIV co-infection in Vietnam



Q.M. Trinh<sup>a,b,c,\*</sup>, H.L. Nguyen<sup>d</sup>, T.N. Do<sup>d</sup>, V.N. Nguyen<sup>e</sup>, B.H. Nguyen<sup>e,f</sup>, T.V.A. Nguyen<sup>c</sup>,  
V. Sintchenko<sup>a,b</sup>, B.J. Marais<sup>a</sup>

<sup>a</sup> Marie Bashir Institute for Infectious Diseases and Biosecurity (MBI), The University of Sydney, Sydney, Australia

<sup>b</sup> NSW Mycobacterium Reference Laboratory, Centre for Infectious Disease and Microbiology – Public Health, ICPMR, Westmead Hospital, Sydney, Australia

<sup>c</sup> Vietnam National Institute of Hygiene and Epidemiology, Hanoi, Vietnam

<sup>d</sup> Vietnam Administration of HIV/AIDS Control, Hanoi, Vietnam

<sup>e</sup> Vietnam National TB Program, Hanoi, Vietnam

<sup>f</sup> International Union Against Tuberculosis and Lung Diseases, Paris, France

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### ABSTRACT

Tuberculosis (TB) and human immunodeficiency virus (HIV) infection are leading causes of disease and death in Vietnam, but TB/HIV disease trends and the profile of co-infected patients are poorly described. *Methods:* We examined national TB and HIV notification data to provide a geographic overview and describe relevant disease trends within Vietnam. We also compared the demographic and clinical profiles of TB patients with and without HIV infection.

*Results:* During the past 10 years (2005–2014) cumulative HIV case numbers and deaths increased to 298,151 and 71,332 respectively, but access to antiretroviral therapy (ART) improved and new infections and deaths declined. From 2011–2014 routine HIV testing of TB patients increased from 58.9% to 72.5% and of all TB patients diagnosed with HIV in 2014, 2,803 (72.4%) received ART. The number of multidrug resistant (MDR)-TB cases enrolled for treatment increased almost 3-fold (578 to 1,532) from 2011–2014. The rate of HIV co-infection in MDR and non-MDR TB cases (51/1,532; 3.3% vs 3,774/100,555; 3.8%; OR 0.77, 95% CI 0.7–1.2) was similar in 2014.

*Conclusions:* The care of TB/HIV co-infected patients have shown sustained improvement in Vietnam. Rising numbers of MDR-TB cases is a concern, but this is not “driven” by HIV co-infection.

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### 1. Introduction

Tuberculosis (TB) and human immunodeficiency virus (HIV) infection present major global health challenges. Their mutually detrimental effect has been well documented and is most evident in Sub-Saharan Africa.<sup>1,2</sup> Of all TB cases identified in 2014, 1.2 million (12%) were co-infected with HIV and 0.4 million TB-related deaths were reported in people living with HIV.<sup>3</sup> Increasing rates of multidrug resistant (MDR)-TB and TB/HIV co-infection place a tremendous strain on public health resources and complicate TB control efforts.<sup>3</sup> TB/HIV co-infection has not been considered a major driver of the TB epidemic in the Asia-Pacific region, but a slowly increasing proportion of TB/HIV co-infected patients has been documented, despite recent reductions in TB case numbers.<sup>4,5</sup>

In 2014, Vietnam was one of the high TB burden countries within the Asia-Pacific region, ranking 11th among the 22 highest TB burden countries in the world.<sup>3</sup> TB is the second most common infectious cause of death in Vietnam, after respiratory infections in general, with 100,349 new and recurrent TB cases and 17,000 TB deaths recorded in 2014.<sup>3</sup> Vietnam has made significant progress in its TB control efforts, achieving Millennium Developmental Goal (MDG) targets for reductions in TB incidence, prevalence and mortality well before the 2015 target date.<sup>6</sup> However, rising numbers of MDR-TB patients is a major concern; Vietnam is ranked 14th among the 27 highest MDR-TB burden countries in the world.<sup>3</sup>

The first case of HIV in Vietnam was detected in 1990.<sup>7</sup> After an initial delay in acknowledging and recognizing the full extent of the problem, Vietnam has made significant efforts to address the HIV/AIDS epidemic. Worryingly the HIV prevalence among high-risk populations remains high in several cities and provinces, with increasing rates of HIV infection among men who have sex with men.<sup>8</sup> In addition, Vietnam is witnessing a change in HIV transmission patterns with increasing numbers of heterosexually transmitted HIV

\* Corresponding author at: Tuberculosis Laboratory, Vietnam National Institute of Hygiene and Epidemiology, No 1 Yersin Street, Hai Ba Trung District, Hanoi, 10000, Vietnam. Tel.: +84 983110183.

E-mail address: [qtri6675@uni.sydney.edu.au](mailto:qtri6675@uni.sydney.edu.au) (Q.M. Trinh).

cases.<sup>9,10</sup> In recent years, enhanced provision of antiretroviral therapy (ART) and isoniazid preventive therapy (IPT) helped to reduce the number of TB/HIV co-infected patients in Vietnam,<sup>11</sup> but despite the progress made TB and HIV remain leading causes of disease and death. Data from the HIV and TB control programmes have never been combined to provide a comprehensive overview of the problem, assess disease trends and describe the profile of TB/HIV co-infected patients in Vietnam. In this report we examined national TB and HIV notification data to provide a geographic overview and describe recent disease trends within Vietnam.

## 2. Methods

The cumulative number of HIV-infected cases, number of patients on ART and IPT, as well as the number of newly diagnosed HIV-infections and deaths over a 10-year period (2005–2014) were reviewed using HIV program data. In addition, we analysed routine notification data collected by the national TB program in Vietnam over a 4-year period (2011–2014). We assessed geographic patterns of disease in 2014, by mapping the TB incidence, HIV prevalence and total number of TB/HIV co-infected patients notified in each province. We compared the profiles of TB patients with and without HIV infection by combining more detailed HIV and TB programmatic data from the 2011–2014 period. Descriptive and comparative statistics was performed using Stata v.13 (Stata Corporation, Texas, USA). Odds ratios and 95% confidence intervals (CI) were calculated using Chi2 test and StatCalc function in Epi Info 7 ([wwwn.cdc.gov/epiinfo/](http://wwwn.cdc.gov/epiinfo/)).

## 3. Results

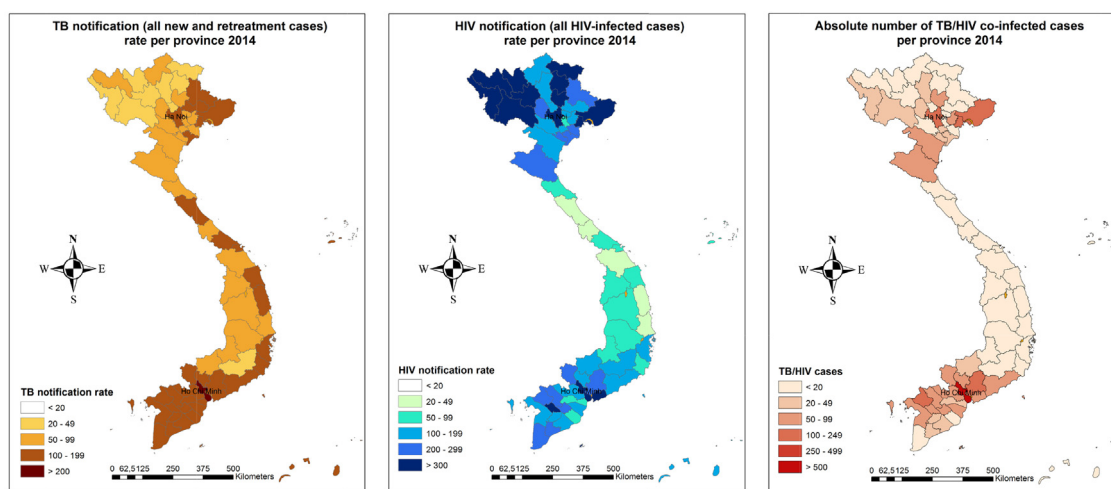
TB notification rates were highest in the Southern provinces of Vietnam, especially in Ho Chi Minh City and the greater Mekong River Delta where incidence rates exceeded 200/100,000 population. TB rates were lowest in the Northern mountainous provinces and central highland areas (<50/100,000 population). In contrast, HIV prevalence rates were high in the Northern mountainous provinces. The greatest absolute numbers of TB/HIV co-infected patients were identified in and around the two biggest metropolitan areas (Ho Chi Minh City and Ha Noi), with the Northeastern coastal province of Quang Ninh also displaying high rates of TB, HIV and TB/HIV co-infection. [Figure 1](#) provides an overview of TB and HIV notification rates in different provinces of Vietnam during

2014, together with the absolute number of TB/HIV co-infected patients per province.

[Figure 2](#) indicates the cumulative number of HIV-infected patients over a 10-year period (2005–2014), together with the number of patients receiving ART, the number of new HIV infections and the number of HIV-related deaths occurring in each year. At the end of 2014, cumulative HIV-infected cases and HIV-related deaths were 298,151 and 71,332 respectively. Annual HIV infections peaked in 2007 with 30,846 new cases and decreased gradually to 11,680 cases in 2014. The annual number of deaths attributed to HIV decreased from 7,885 to 2,146 over the 10-year period. ART coverage has been expanded and late ART initiation (CD4 <100 cells/mm<sup>3</sup>) has been reduced from 63% (2009) to 34.4% (2014). IPT has been made available to HIV-infected patients in Vietnam from 2009. The cumulative number of patients who received IPT increased from 320 in 2009 to 46,607 in 2014, accounting for 15.6% (46,607/298,151) of current HIV cases.

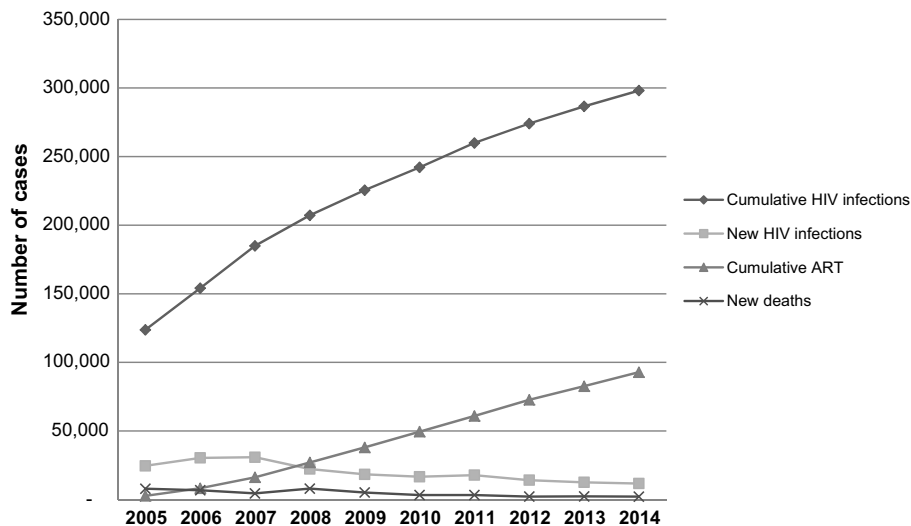
Vietnam National Tuberculosis Program data indicate that TB case notifications changed little from 2011–2014, with 100,518 cases in 2011 and 102,087 cases in 2014. During that period, the number of TB patients tested for HIV infection increased from 58.9% to 72.6% of recorded cases ([Figure 3](#)). With the increased number of tests performed, the proportion of HIV-infected patients among those tested declined from 8.0% in 2011 to 5.2% in 2014. Over the same time period the percentage of HIV-infected TB patients receiving ART increased from 48.6% to 72.3% of cases.

Key characteristics of TB patients diagnosed between 2011–2014, with and without HIV co-infection, are compared in [Table 1](#). Compared to HIV uninfected patients a higher percentage of HIV co-infected TB cases were diagnosed with extra-pulmonary TB [1,276 (28.7%) vs 12,628 (19.8%); Odds Ratio (OR) 1.6, 95% Confidence Interval (CI) 1.5–1.7]; and less were sputum smear positive [2,245 (50.4%) vs 38,581 (60.4%); OR 0.7 (95% CI 0.6–0.7)]. Among sputum smear-positive TB cases, more HIV co-infected patients presented as retreatment cases than HIV-uninfected patients, and less as new cases [1,773 (79.0%) vs 32,827 (85.1%); OR 0.7 (95% CI 0.6–0.7)]. Most retreatment occurred after TB recurrence [7,090/8,853 (80.1%) of retreatment cases], which was more common among HIV-infected patients, as were retreatment after treatment failure and treatment interruption ([Table 1](#)). Interestingly, among MDR-TB cases a higher percentage of HIV co-infected patients presented as new cases [6 (15.0%) vs 30 (4.0%); OR 4.2 (95% CI 1.6–10.8)] compared to HIV-uninfected patients, although case numbers were small.



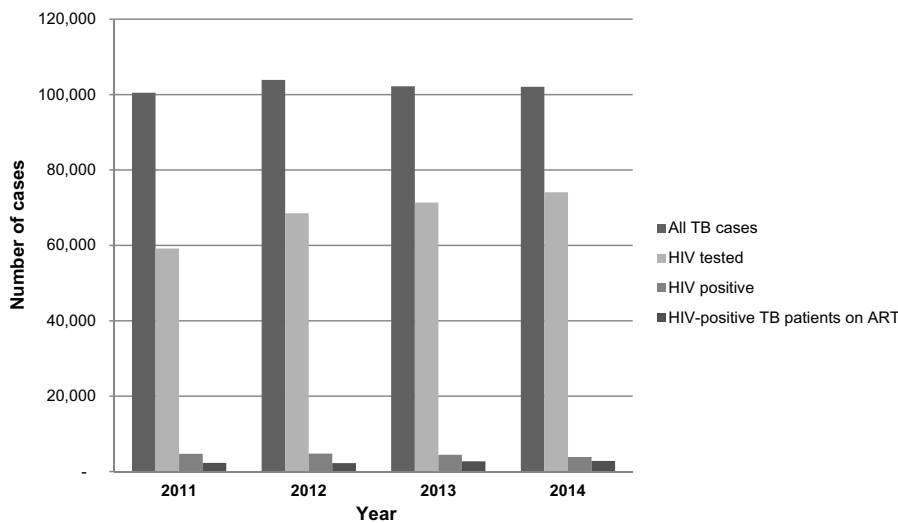
TB – tuberculosis; HIV – Human immunodeficiency virus;

**Figure 1.** Provincial TB and HIV notification rates in Vietnam (2014), with absolute number of TB/HIV co-infected patients in care.



HIV – Human immunodeficiency virus; ART – Antiretroviral Therapy

**Figure 2.** Cumulative number of HIV-infected patients and antiretroviral therapy use in Vietnam, with number of new HIV infections and HIV-related deaths (2005–2014).



TB – tuberculosis; HIV – Human immunodeficiency virus; ART – Antiretroviral Therapy

**Figure 3.** Number of tuberculosis cases tested for HIV and receiving antiretroviral therapy in Vietnam (2011–2014).

The average annual number of MDR-TB cases was 965, representing 0.9% of all cases. The greatest number of MDR-TB cases occurred among treatment failures (especially category 2 failures) and patients retreated for a second TB episode (TB recurrence). The overall percentage of TB cases with MDR disease was less among HIV co-infected patients (40/4,452; 0.9%) than among HIV-uninfected patients [(743/63,868; 1.2%; OR 0.77; 95% CI 0.6–1.1)]. Figure 4 summarizes the number of patients diagnosed with MDR-TB and enrolled for treatment, which increased from 578 cases in 2011 to 1,532 cases in 2014. Throughout this period the number of HIV co-infected patients among MDR-TB cases remained low, with only 51 (3.3%) MDR-TB/HIV co-infected patients identified in 2014.

#### 4. Discussion

With increased HIV testing during the study period, the proportion of HIV-infected patients among those tested declined from 8.0% in 2011 to 5.2% in 2014.<sup>3,6,12,13</sup> This is lower than TB/HIV

co-infection rates in sub-Saharan Africa where rates in excess of 50% are reported, but similar to TB/HIV co-infection rates in India (4%) and Cambodia (3%). Within other high TB burden countries in Asia, TB/HIV co-infected rates in Indonesia (16%), Thailand (13%) and Myanmar (11%) are higher, but lower in China (2%) and the Philippines (<1%).<sup>3</sup> However, HIV testing rates in these countries are highly variable, with greatly reduced confidence in the TB/HIV co-infection rates reported from countries with low testing rates.

Within Vietnam the highest TB/HIV co-infection rates were found in the two big metropolitan areas, Ho Chi Minh City and Ha Noi. Interestingly HIV/AIDS prevalence rates were high in the remote Northern provinces, although TB/HIV co-infection rates were relatively low. High HIV infection rates may be a legacy of poverty among remote tribal groups, commercial sexual exploitation and movement across the Chinese border,<sup>7,14,15</sup> while relatively low rates of TB/HIV co-infection rates may reflect lower rates of HIV testing among TB patients and reduced access to TB and HIV services.<sup>16</sup> The Northeastern coastal province of Quang Ninh reported high TB, HIV and TB/HIV co-infection rates, which

**Table 1**  
Comparison of tuberculosis patients with and without HIV co-infection in Vietnam (2011–2014)

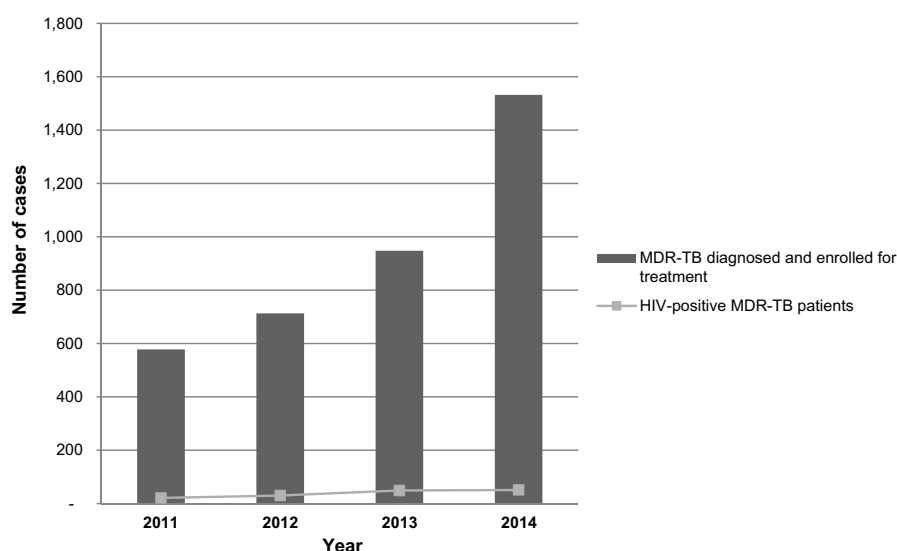
	All n (%)	HIV uninfected n (%)	HIV co-infected n (%)	HIV status unknown n (%)	OR (95% CI) <sup>*</sup>
<b>All TB</b>					
Pulmonary TB sm+	59 435 (58.2)	38 581 (60.4)	2 245 (50.4)	18 609 (55.0)	0.7 (0.6 - 0.7)
Pulmonary TB sm–	21 288 (20.8)	12 659 (19.8)	931 (20.9)	7 698 (22.7)	1.1 (1.0 - 1.2)
Extra-pulmonary TB	21 459 (21.0)	12 628 (19.8)	1 276 (28.7)	7 555 (22.3)	1.6 (1.5 - 1.7)
Total (N)	102 182	63 868	4 452	33 862	
<b>Pulmonary TB sm+</b>					
New	50 582 (85.1)	32 827 (85.1)	1 773 (79)	15 982 (85.9)	0.7 (0.6 - 0.7)
Retreatment after recurrence	7 090 (11.9)	4 630 (12.0)	343 (15.3)	2 117 (11.4)	1.3 (1.2 - 1.5)
Retreatment after treatment failure	573 (1.0)	394 (1.0)	37 (1.6)	142 (0.8)	1.6 (1.2 - 2.3)
Retreatment after treatment interruption	453 (0.8)	264 (0.7)	34 (1.5)	155 (0.8)	2.2 (1.6 - 3.2)
Other AFB(+)	737 (1.2)	466 (1.2)	58 (2.6)	213 (1.1)	2.2 (1.6 - 2.9)
Total (N)	59 435	38 581	2 245	18 609	
<b>MDR-TB</b>					
New	53 (5.0)	30 (4.0)	6 (15.0)	17 (9.3)	4.2 (1.6 - 10.8)
Failure Cat 1	172 (17.8)	139 (18.7)	6 (15.0)	27 (14.8)	0.8 (0.3 - 1.9)
Failure Cat 2	382 (39.6)	318 (42.8)	13 (32.5)	51 (28.0)	0.6 (0.3 - 1.3)
TB recurrence	298 (30.9)	212 (28.5)	12 (30.0)	74 (40.7)	1.1 (0.5 - 2.2)
Default	22 (2.3)	16 (2.2)	2 (5.0)	4 (2.2)	2.4 (0.5-10.8)
Other	38 (3.9)	28 (3.8)	1 (2.5)	9 (4.9)	0.7 (0.1 - 4.9)
Total (N)	965	743	40	182	

sm+ = sputum smear-positive; sm– = sputum smear-negative.

Cat 1 – first-line treatment regimen (isoniazid, rifampicin, pyrazinamide, ethambutol); (2 HRZE/4 HRE).

Cat 2 – retreatment regimen; Cat 1 with added streptomycin (2 SHRZE/1 HRZE/5H3R3E3).

<sup>\*</sup> OR – Odds Ratio of in HIV-infected compared to HIV-uninfected, excluding data of those with unknown HIV status.



HIV – Human immunodeficiency virus; MDR-TB – Multidrug-resistant tuberculosis

**Figure 4.** Multidrug resistant tuberculosis cases enrolled for treatment in Vietnam and HIV co-infection status (2011–2014).

may be linked to its position as a special economic zone with lots of cross-border people movement, access through its multiple seaports and tourism related to the World Heritage status of Ha Long Bay.

Despite recent progress nearly a third of TB patients did not receive a HIV test in 2014 and of those known to be HIV-infected, less than three quarters (73%) received ART.<sup>3</sup> Compared to ART provision for TB/HIV co-infected patients in other high TB burden countries in the region Cambodia (98%), India (90%) and Myanmar (90%) are doing better than Vietnam, but China (69%), Thailand (69%), the Philippines (49%) and Indonesia (26%) are faring worse.<sup>3</sup> Unfortunately many TB/HIV co-infected patients initiated on ART were lost to follow up, especially after TB treatment conclusion. This is a major concern and better patient support strategies are required to ensure on-going ART beyond TB treatment completion. We were unable to assess active TB case finding in people living

with HIV, since this data is not reliably reported at present. Links between the TB and HIV programmes should be strengthened to ensure optimal bi-directional screening and long-term treatment adherence.

To address these issues, the Government of Vietnam has issued Guidelines for Collaboration between the National TB and HIV programs and established a TB/HIV Coordinating body at the central and provincial levels to implement interventions aimed at decreasing the TB burden among people living with HIV and ensure optimal HIV care in patients diagnosed with TB. IPT provision has improved with nearly 50,000 HIV-infected patients receiving IPT in 2014.<sup>16</sup> About 70–75% of TB/HIV co-infected patients received ART, which remains well off target. It is hoped that this will improve further since TB/HIV service delivery has now been integrated within Provincial, District and Commune Preventive Health Centers.

The total number of people living with HIV in Vietnam continues to rise, but this is a function of improved access to ART and increased survival rather than an excessive number of new infections. However, everything possible should be done to limit new HIV infections to zero. Timely ART initiation will require outreach to key populations, integration of HIV testing into methadone maintenance programmes and decentralized HIV testing and care. During the study period HIV testing and counselling services were primarily funded by international donors. Given strong economic growth and recent recognition of Vietnam as a middle-income country, the Government of Vietnam needs to identify domestic funding sources to sustain and expand HIV services into the future.<sup>17</sup> In September 2015 the WHO released new ART guidelines recommending ART initiation in all HIV-infected individuals, irrespective of TB co-infection, clinical disease stage or CD4 cell count.<sup>18</sup> This has yet to be implemented in Vietnam.

With assistance from the Global Fund there has been rapid scale-up of programmatic MDR-TB management since 2009, with more than 1,500 patients enrolled in MDR-TB treatment during 2014.<sup>16</sup> The degree of treatment scale-up has been impressive, but maintaining high numbers of patients on MDR-TB treatment will require continued commitment and sustained funding. Luckily the number of HIV-infected patients with MDR-TB remains small and the MDR-TB epidemic is essentially independent of HIV co-infection in Vietnam; similar to the situation in Eastern Europe,<sup>19</sup> but in contrast to what has been observed in some sub-Saharan African settings.<sup>20</sup>

High rates of HIV co-infection does have the potential to fuel the MDR-TB epidemic, especially in settings with high rates of transmitted MDR-TB.<sup>2,21</sup> The fact that MDR-TB cases were mainly identified among patients who failed TB treatment and among retreatment cases may suggest that resistance acquisition is a major contributor, but it is important to consider the strong selection biases. Current testing protocols prioritize retreatment cases and those who fail treatment for MDR-TB work-up. The experience from Mongolia, Russia and South Africa suggest that the majority of these patients likely represent transmitted MDR-TB, even though they had previous TB treatment exposure.<sup>22–24</sup> MDR-TB was detected with increased frequency among TB/HIV co-infected patients that presented as new cases, which raise additional MDR-TB transmission concerns in this group and emphasize the need for enhanced infection control in settings that provide joint TB and HIV services.

Some limitations of this study should be acknowledged. The data employed in this review represent routine programmatic data with some missing data and discordance between the TB and HIV programmes. We were unable to conduct detailed demographic analysis of TB patients with and without HIV co-infection or comparisons of HIV-infected patients with and without previous TB treatment due to lacking information. Despite these limitations, the data sets analysed provide important real-life data and represent the most comprehensive overview of overlapping TB and HIV disease burdens in Vietnam, and reflect some objective parameters for monitoring of integrated healthcare service delivery performance.

In conclusion, TB/HIV co-infection is relatively uncommon (~5% of TB cases) in Vietnam and HIV infection is not a major driver of rising MDR-TB rates. This is different to sub-Saharan Africa and countries such as Swaziland that report TB/HIV co-infection rates exceeding 80%, with high rates of MDR-TB among co-infected cases.<sup>25</sup> Irrespective of HIV co-infection rates, the global rise of MDR-TB seems to be driven by primary transmission of drug resistant strains.<sup>26,27</sup> Although the cumulative number of HIV-infected patients continues to increase in Vietnam, new

HIV-infections and HIV-related deaths are on the decline. Integrated TB/HIV services are improving, but greater effort and more domestic funding are required to close the gap between service delivery indicators and global targets, with special focus on the hot-spot areas identified.

*Conflict of interests:* None to declare.

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