Original Article

High Rates of Human Immunodeficiency Virus and Drug Resistance in Tuberculosis Patients in Manila, Philippines

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Abstract

Background: The incidence of tuberculosis (TB) in the Philippines is 288/100,000 populations (2014), wherein 2% of new cases and 21% of retreatment cases are multidrug-resistant TB (MDR-TB). In addition, the rate of human immunodeficiency virus (HIV) infection has been alarmingly over the past 7 years in the subpopulation of men who have sex with men in the Philippines. In June 2016, there were 841 new HIV-seropositive individuals reported to the HIV/AIDS and Antiretroviral Therapy Registry of the Philippines. In the present study, we aimed to investigate the prevalence of HIV among MDR-TB patients in a Manila hospital from 2011 to 2015. **Subjects and Methods:** TB patients who referred to the programmatic management of drug-resistant TB (2012 to 2015) were tested for MDR-TB (using Xpert MTB/RIF assay) and HIV infection. In addition, the available data that belong to patients before the introduction of the Xpert MTB/RIF assay were included. **Results:** A total of 4515 presumptive drug-resistant TB patients were screened (2012–2015) to determine the percentage of MDR-TB cases: 16% (2012), 14% (2013), and 11% (2014 and 2015). Among the MDR-TB patients, the percentage of HIV-positive cases increased yearly: 0.5% (2011), 3% (2012), 5% (2013), 9% (2014), and 15% (2015). The high mortality rate ranged from 42% to 66%. The cure rate among the enrolled MDR-TB cases was 47% in 2012, which increased from 27% in 2011, but it did not improve thereafter (46% in 2013 and 51% in 2014). **Conclusions:** A remarkable increase in the prevalence of HIV among MDR-TB patients was found. The raises are alarming and need urgent attention on different risk factors and/or living style of patients.

Keywords: Adverse reaction, multidrug-resistant- tuberculosis, Xpert MTB/RIF

Introduction

Although the World Health Organization (WHO) has expressed the ambition to decrease the incidence of tuberculosis (TB) substantially over the coming decades, this target is hampered by evolving resistance and, in some geographic areas, frequent coinfection with human immunodeficiency virus (HIV). In 2015, an estimated 10.4 million new TB cases were recorded worldwide, including an estimated 480,000 new cases of multidrug-resistant-TB (MDR-TB) and an additional 100,000 cases of rifampicin-resistant TB (RR-TB), which are also eligible for MDR-TB treatment.[1] The National TB Control Program in the Philippines reported that, compared to 2003, the number of persons with TB symptoms examined increased by 82% in 2011.[2] The 2nd National Drug Resistance Survey in the Philippines (2011–2012) showed that 1.96% of new and 21.4% of the retreatment cases were MDR-TB. The results also revealed that resistance to two or more anti-TB drugs was far more common than monoresistance to a particular drug in the Philippines.[3] In South Africa, the number of deaths caused by acquired immune deficiency syndrome (AIDS)-TB in 1990 accounted for 47% of all deaths, and an increase in HIV infections was also noted during this year.[4] Moreover, extensively drug-resistant-TB emerged and was reported for the first time in a society in KwaZulu-Natal in South Africa.[5,6] We previously described the manner in which

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an AIDS/TB endemic can be considered a natural disaster.[7] In the Philippines, the rate of HIV infection has markedly increased over the past 7 years among the subpopulation of men who have sex with men.[8] Research on the molecular diagnosis of drug-resistant TB facilitated the development of the Xpert MTB/RIF and line probe assays, both of which efficiently identify RR- and MDR-TB.[9] The National TB program in the Philippines introduced the GeneXpert MTB/RIF assay in San Lazaro Hospital (SLH) in Manila, Philippines, as recommended by the WHO.[10-12] In the present study, we describe the trends in HIV infections in combination with the emergence of MDR-TB over the 5-year period from 2011 to 2015.

Subjects and Methods

Hospitals

The SLH is a 500-bed tertiary referral hospital for infectious diseases in Manila, Philippines, and offers 100 beds for the treatment of regular TB patients and 20 beds for MDR-TB patients. Since December 2011, patient samples have been examined using the Xpert MTB/RIF assay, to detect drug resistance at the time of diagnosis.

Diagnosis

Diagnostic samples were collected based on the clinical policy at the hospital, and all sample types were eligible for inclusion in this study, including gastric aspirate/bronchoalveolar lavage, sputum, cerebral spinal fluid, nasopharyngeal aspirate, lymph node aspirate, and tissue.

Sample processing

All samples were decontaminated by the conventional procedures using NALC-NaOH, as described previously.[13] All sample pellets were divided for smear microscopy, drug susceptibility testing (DST), and the Xpert MTB/RIF assay. The technicians who interpreted the Xpert MTB/RIF assays were blinded to the clinical data and the other test results.

Ziehl–Neelsen smear

Two drops of sample pellet (approximately 200 µl) were used for smear microscopy of the Ziehl–Neelsen staining according to the WHO standard protocol.[14]

Drug susceptibility testing

The first positive culture from each patient was subjected to phenotypic DST for the first-line TB drugs using the 1% proportional method on Löwenstein–Jensen media (Canetti). The critical concentrations used were 0.2 µg/ml for isoniazid, 4 µg/ml for streptomycin, 40 µg/ml for rifampicin, and 2 µg/ml for ethambutol. For pyrazinamide resistance testing, the Wayne method was applied using the critical concentration 200 µg/ml at the National TB Reference Laboratory, Philippines.[3,15,16]

Xpert MTB/RIF assay

Each sample (0.5 ml) was treated with 1.5 ml of sample reagent and processed according to the manufacturer's standard operating procedure (Cepheid, USA).[15]

Human immunodeficiency virus infection

The sera from MDR-TB patients from 2011 to 2015 were tested for anti-HIV antibodies at the STD AIDS Cooperative Center Laboratory using an immune chromatography kit for the HIV antibody (Sysmex, Kobe, Japan). If the findings were positive, the result was confirmed by polymerase chain reaction (Roche, CA, USA) and/or western blotting (MP Biomedicals, CA, USA).

Treatment

When a sample exhibited an RR-TB profile in the Xpert MTB/RIF assay, the patient was considered to have MDR-TB. Accordingly, standardized regimen A (SRA), which included pyrazinamide (Z), kanamycin (Km), levofloxacin (Lfx), prothionamide (Pto), and cycloserine (Cs), was administered to patients with relapse and those with only one previous treatment, whereas standardized regimen B (SRB), which included ZKmLfxPtoCs and para-aminosalicylic acid (Pas), was administered to patients with a history of more than one previous treatment;[17] after 2012, ZKmLfxPtoCs was the standardized regimen given to all patients.[16] The TB treatment outcomes were defined according to the WHO standards as "cured, treatment completed, default, transfer out, or died."[16]

Patients

In 2011: A total of 186 TB patients were enrolled in this cohort. The retreatment cases were scheduled to receive SRA or SRB according to their DST results. Once the baseline DST results were found to be positive for RR/isoniazid resistant (HR), the patients were classified as having bacteriologically confirmed RR (BC-RR)/MDR-TB and treatment was continued for 18 to 24 months. If the baseline DST results revealed susceptibility to all first-line drugs or if the TB culture was negative or if no DST results were available, the patients were excluded from the analysis and referred back to the referring health facilities. Patients with clinically diagnosed (CD)-MDR-TB had negative TB cultures and were assessed by the physician to continue the empiric MDR-TB regimen (SRA/SRB).

In 2012–2014: The cohort from these 4 years was primarily enrolled based on the findings of the Xpert MTB/RIF assay, with which all presumptive drug-resistant TB patients were tested. All patients with RR-TB, as detected in the Xpert MTB/RIF assay, were categorized as having MDR-TB. This reduced the enrollment of empirically treated or CD-MDR-TB patients.

In 2015: The numbers of screened samples decreased over the last two-quarters, probably due to the establishment of other local health centers.

Detection of human immunodeficiency virus among multidrug-resistant tuberculosis patients

Patients with HIV-positive MDR-TB were referred to the PMDT treatment center for the prompt initiation of treatment, regardless of their CD4 T-cell counts. HIV-positive patients with drug-susceptible TB were similarly referred to SLH DOTS for the prompt initiation and monitoring of treatment.

Ethics

This report describes secondary data from clinical records from the SLH without any direct patient identifiers. This study is descriptive and no intervention was made in regular patient diagnostics or treatment.

Results

Treatment outcome

In 2011, 186 TB cases were enrolled in the study: 41% ($n = 77$) had MDR-TB as confirmed by DST, 56% ($n = 104$) had CD-MDR-TB, and 3% ($n = 5$) had monoresistant TB. We assessed the treatment outcomes for the BC-MDR-TB cases ($n = 77$): 27% ($n = 21$) were cured, 13% ($n = 10$) completed treatment (treatment success rate, 40%), 21% ($n = 16$) died, 1% ($n = 1$) failed, and 38% ($n = 29$) were lost to follow-up. Of the 45 CD-MDR-TB patients (after 59 were excluded from the analysis), 7% ($n = 3$) were cured, 20% ($n = 9$) completed treatment, 11% ($n = 5$) died, and 62% ($n = 28$) were lost to follow-up. Moreover, of the patients with isoniazid monoresistant TB, one completed treatment, two died, and two were lost to follow-up [Table 1]. The reasons for lost to follow-up included financial limitations, inaccessibility, adverse drug reactions, and attitude or behavioral problems. Most of the patients who died were critically ill and were admitted to the SLH MDR-TB ward following their diagnosis and initiation of treatment. In 2012, 2013, and 2014, 1083, 1101, and 1279 patients, respectively, were screened and tested with the Xpert MTB/RIF assay. Of these, 171 (16%), 153 (14%), and 146 (11%), respectively, were confirmed to have RR-TB. The treatment success rate was 40% in 2011 and improved to 49% in both 2012 and 2013. The proportion of patients who were lost to follow-up was 38% in 2012 and 34% in 2013, and the underlying reasons were similar to those in 2011 [Table 1]. Among all the cases in 2015 who were presumptively screened for TB ($n = 1052$), 122 (11%) were found to have RR-TB. Of these, 73% ($n = 90$) were enrolled in either the SLH PMDT treatment center or in another treatment/satellite treatment center [Table 1]. However, 27% ($n = 32$) of RR-TB patients who were identified using the Xpert MTB/RIF assay were not enrolled: 10% ($n = 12$) refused to revisit for enrollment after phone calls and home visits, 8% ($n = 10$) died within 2 weeks of diagnosis, 7% ($n = 8$) could not be located/relocated, and 2% ($n = 2$) were treated with first-line drugs at the local health center, despite the diagnosis of RR-TB. Despite ongoing treatment, approximately 18% ($n = 16$) of the 90 RR-TB patients enrolled in treatment centers died, and 25% ($n = 23$) were lost to follow-up [Table 1, partial outcome results]. Their causes of death were sepsis, probably due to MDR-TB, 38% (6/16); sepsis secondary to AIDS and/or MDR-TB, 32% (5/16); cor pulmonale, 12% (2/16); one case (6%) of either chronic hypoxic encephalopathy, acute myocardial infarct, or asphyxia.

Adverse drug reactions

Major adverse drug reactions were only reported in the second half of 2015. Minor adverse drug reactions were recorded on the patients' progress report forms, whereas severe adverse events

Table 1: Treatment outcome of drug resistant tuberculosis patients during 2011-2015

Enrolled DR-TB#	Classification	Cured, *n* (%)	Completed, *n* (%)	Died, *n* (%)	Failed, *n* (%)	Lost to follow, *n* (%)	Ongoing, *n* (%)	Excluded, *n* (%)	Total
2011 *n*=186 (36th month)									
n=77	BCRR	21 (27)	10 (13)	16 (21)	1 (1)	29 (38)	0	0	77
n=104 (56%)	CD-RR	3 (7)	9 (20)	5 (11)	0	28 (62)	0	59 (57)	45
n=5	Other DxR	0	1 (20)	2 (40)	0	2 (40)	0	0	5
2012 *n*=198 (36th month)									
n=180	BCRR	85 (47)	3 (2)	24 (13)	0	68 (38)	0	0	180
n=9	CD-RR	1 (11)	3 (33)	2 (22)	0	3 (33)	0	0	9
n=9	Other DxR	4 (44)	0	0	0	5 (56)	0	0	9
2013 *n*=113 (36th month)									
n=112	BCRR	51 (46)	3 (3)	17 (15)	2 (2)	39 (34)	0	0	112
n=1	Other DxR	1 (100)	0	0	0	0	0	0	1
2014 *n*=106 (24th month)									
n=104	BCRR	55 (51)	2 (2)	12 (12)	0	32 (30)	3 (5)	0	104
n=1	CD-RR	1 (100)	0	0	0	0	0	0	1
n=1	Other DxR	0	1 (100)	0	0	0	0	0	1
2015 *n*=95 (partial report)									
n=90	BCRR	14 (15)	0	16 (18)	0	27 (30)	33 (36)	0	90
n=4	CD-RR	0	1 (25)	0	0	2 (50)	1	0	4
n=1	Other DxR	0	1 (100)	0	0	0	1 (100)	0	1

BC-RR in 2011 was assessed by DST while after December 2011 were done by GeneXpert. BCRR: Bacteria confirmed rifampicin positive TB confirmed by DST/GeneXpert, CD-RR: Clinically diagnosed rifampicin positive TB, Other Dx R: Other drug resistant, TB: Tuberculosis, DR-TB: Drug-resistant tuberculosis, DST: Drug susceptibility testing

were reported to the Food and Drug Administration (FDA) through the Department of Health in the Philippine.[15] Serious adverse events included hypokalemia and behavioral changes. A total of 7% of patients required hospitalization for intravenous potassium replacement [Table 2].

Increased human immunodeficiency virus detection among multidrug-resistant tuberculosis patients from 2011 to 2015 at the San Lazaro Hospital

There has been increase in the detection of HIV-positive MDR-TB patients from 2011 ($n = 1$) to 2015 ($n = 14$). A total of 37 cases were identified, and the identification rate gradually increased over time: 0.5% in 2011, 3% in 2012, 5% in 2013, 9% in 2014, and 15% in 2015 [Table 3]. The HIV-positive rate among MDR-TB patients was increased 30-fold in 2015, compared to the rate in 2011, and the administration of antiretroviral therapy or co-trimoxazole preventive therapy (CPT) was initiated for treatment and prevention. The treatment outcomes are summarized in Table 4. The mortality rate was high among the AIDS/MDR-TB patients and ranged from 36% to 67% (average, 46%). The cause of death was primarily severe sepsis or meningitis. Among the cases with fatal outcomes, only two were started on ART before death [Table 4].

Discussion

In the present report, we found an increase in HIV infection and a high prevalence of RR-TB among TB patients at the SLH in Manila during the study-years (2011–2015). The 2014 Nationwide Drug Resistance Survey in the Philippines indicated that, among notified TB cases, 2% of new cases and 21% of retreatment cases were MDR-TB cases [Table 4].[15] Our data in 2015 showed that, of a total of 1052 cases, 11.6% had RR-TB, indicating high rates of drug-resistant TB in the Philippines. The increase of cure rate of BC-RR/MDR-TB for 2011 (26%) was apparently lower than that in 2012 (47%), 2013 (46%), and 2014 (44%), and the mortality rate also decreased from 21% in 2011 to 13% in 2012, 15% in 2013, and 12% in 2014. These findings indicate that the introduction of the Xpert MTB/RIF assay contributed to early detection and the exclusion of non-MDR cases. The loss to follow-up rate was high (38%–34%) and may be the major reason for the low success rate. The apparent decrease in the enrolled cases in 2013 ($n = 112$), as compared to that in 2012 ($n = 179$), was due to the relocation of patients to other developed treatment centers. Studies in Algeria showed that all of the RR strains identified by the Xpert MTB/RIF assay were phenotypically confirmed as MDR-TB strains.[18] In another study in Ghana, DST analysis of the seven cases of RR-TB found by Xpert MTB/RIF showed that six exhibited further drug resistance and five of these were MDR-TB.[17] With regard to rifampicin, monoresistance was noted in only 3.8%, as compared to 26.45% noted for any resistance to rifampicin in the same group of patients in the Philippines.[3] These findings support the proposal of administering the recommended MDR-TB regimen for any patient with RR-TB for whom isoniazid resistance is absent or unknown.[19] However, the cure rate has remained low (44%–47%) as reported elsewhere.[20] The factors associated with loss to follow-up during treatment for MDR-TB in the Philippines include adverse reactions and alcohol abuse.[20] In addition, we believe that more detailed DST results would be necessary to develop new strategies against TB as we recently found that 13% of MDR-TB isolates in China (in 2009) were fluoroquinolone resistant.[21] The use of recently developed drugs may also increase the cure rate although careful management is necessary.[22] Although the number of HIV cases in the Philippines is relatively low compared to the number in other countries, it has increased rapidly.[1,23] Owing to the high prevalence of TB in the Philippines, we examined the latent TB infection

Table 2: Adverse drug reactions of drug-resistant tuberculosis regimen during 2015 ($n = 255$)

Most common adverse drug reactions/ adverse events	*n* (%)	Reportable	Percentage reported to FDA
Body/muscle/joint pains	67 (26)	Not reportable	-
Allergy	61 (24)	Not reportable	-
Epigastric pain	49 (19)	Not reportable	-
Hypokalemia	29 (11)	Reportable	7 (2/29)
Nausea and vomiting	15 (6)	Not reportable	-
Diarrhea	7 (3)	Not reportable	-
Insomnia	7 (3)	Not reportable	-
Dizziness	7 (3)	Not reportable	-
Vertigo	7 (3)	Not reportable	-
Increased BUN	3 (1)	Not reportable	-
Behavior changes	2 (1)	Reportable	100
Neuropathy	1 (0.5)	Not reportable	-

FDA: Food and Drug Administration, BUN: Blood urea nitrogen

Table 3: Human immunodeficiency virus monitoring results among enrolled multidrug-resistant tuberculosis; patients from 2011-2015

	2011	2012	2013	2014	2015
Enrolled patients	186	198	112	106	95
HIV patients (%)	1 (0.5)	6 (3)	6 (5)	10 (9)	14 (15)
Male (%)	1 (100)	6 (100)	6 (100)	10 (100)	14 (100)

HIV: Human immunodeficiency virus

Table 4: Treatment outcome of HIV + drug resistant TB from 2011 to 2015

Year	# of HIV+	Cured	Completed	Died	Lost to follow	Failed	Ongoing
2011	1	1	0	0	0	0	0
2012	6	2	0	4	0	0	0
2013	6	1	0	3	1	1	0
2014	10	1	0	5	2	0	2
2015	14	0	0	5	3	0	6
Total	37	5	0	17	6	1	8

rates in the Philippines and found that 50% of healthcare workers had a latent TB infection.[24] Offering routine HIV tests to presumptive TB patients would help identify large numbers of previously undetected cases of HIV infection. Several operational challenges have been overcome and offer useful insights into the improvement of HIV test adoption in this important group of patients in India.[13,25] We previously described the genotype of 37 TB patients at SLH all belonged to the Manila type. Furthermore, we reported elevated levels of galectin-9 (Gal-9) in these TB patients.[13] Infection with Manila-type TB has already been reported in a patient in Japan who has never traveled to the Philippines.[26] Moreover, Beijing-type TB, the most prevalent type in East Asia, including Japan, which is known to be associated with resistance to drugs and escape from BCG vaccination,[27] was not detected in our study. An elevation in Gal-9 levels was observed in patients with AIDS/TB,[28] or other acute febrile illnesses, such as acute HIV infection, dengue, and malaria.[28-30] Gal-9 was recently identified as an immune checkpoint molecule, along with its receptor Tim-3.[31] Owing to the emergence of additional cases of drug-resistant TB, it is vital to boost immune responses by manipulating immune molecules and to understand the pathophysiology of MDR-TB infections through future studies. In fact, Gal-9 and its receptors could be used to boost immune responses against MDR-TB as a host-directed therapy.[32]

Conclusion

A remarkable increases in the prevalence of HIV among multidrug-resistant (MDR)-tuberculosis (TB) patients were found. The raises is alarming and needs urgent attention on different risk factors and/or living style of patients.

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Conflicts of interest

There are no conflicts of interest.

References

1. WHO. Global Tuberculosis Report. Geneva Switzerland: WHO; 2015.
2. Vianzon R, Garfin AM, Lagos A, Belen R. The tuberculosis profile of the Philippines, 2003-2011: Advancing DOTS and beyond. Western Pac Surveill Response J 2013;4:11-6.
3. Republic of the Philippines DOH. Second National Drug Resistance Survey on Tuberculosis in the Philippines. Research Institute for Tropical Medicine; 2014.
4. South Africa National DOH. The 2012 National Antenatal Sentinel HIV & Herpes Simplex Type-2 Prevalence Survey. National Department of Health Pretoria; 2013.
5. Mee P, Wagner RG, Gómez-Olivé FX, Kabudula C, Kahn K, Madhavan S, *et al.* Changing use of traditional healthcare amongst those dying of HIV related disease and TB in rural South Africa from 2003-2011: A retrospective cohort study. BMC Complement Altern Med 2014;14:504.
6. Gandhi NR, Moll A, Sturm AW, Pawinski R, Govender T, Lalloo U, *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.
7. Hattori T, Chagan-Yasutan H, Shiratori B, Egawa S, Izumi T, Kubo T, *et al.* Development of point-of-care testing for disaster-related infectious diseases. Tohoku J Exp Med 2016;238:287-93.
8. Epidemiology Bureau DOHP. HIV/AIDS and ART Registry of the Philippines. Epidemiology Bureau, Department of Health; 2016.
9. Aurin TH, Munshi SK, Kamal SM, Rahman MM, Hossain MS, Marma T, *et al.* Molecular approaches for detection of the multi-drug resistant tuberculosis (MDR-TB) in Bangladesh. PLoS One 2014;9:e99810.
10. World Health Organization. Automated Real-Time Nucleic Acid Amplification Technology for Rapid and Simultaneous Detection of Tuberculosis and Rifampicin Resistance: Xpert MT; 2013.
11. World Health Organization. Policy Statement: Automated Real-Time Nucleic acid Amplification Technology for Rapid and Simultaneous Detection of Tuberculosis and Rifampicin Resistance: Xpert MT; 2011.
12. World Health Organization. Laboratory Service in Tuberculosis Control Part II: Microscopy. World Health Organization: Global TB Programme; 1998.
13. Shiratori B, Leano S, Nakajima C, Chagan-Yasutan H, Niki T, Ashino Y, *et al.* Elevated OPN, IP-10, and neutrophilia in loop-mediated isothermal amplification confirmed tuberculosis patients. Mediators Inflamm 2014;2014:513263.
14. World Health Organization. Guidelines for Drug Susceptibility Testing for Second-Line Anti-Tuberculosis drugs for DOTS-Plus; 2001.
15. Republic of the Philippines DOH. National Tuberculosis Control Program: Manual of Procedures. Department of Health; 2014.
16. WHO. Treatment of Tuberculosis: Guidance for National Programmes. World Health Organization: Stop TB Department. Report No. WHO/HTM/TB/2009/420; 2009.
17. Boakye-Appiah JK, Steinmetz AR, Pupulampu P, Ofori-Yirenkyi S, Tetteh I, Frimpong M, *et al.* High prevalence of multidrug-resistant tuberculosis among patients with rifampicin resistance using GeneXpert *Mycobacterium tuberculosis*/rifampicin in Ghana. Int J Mycobacteriol 2016;5:226-30.
18. Guenaoui K, Harir N, Ouardi A, Zeggai S, Sellam F, Bekri F, *et al.* Use of GeneXpert *Mycobacterium tuberculosis*/rifampicin for rapid detection of rifampicin resistant *Mycobacterium tuberculosis* strains of clinically suspected multi-drug resistance tuberculosis cases. Ann Transl Med 2016;4:168.
19. Mateo R Jr., Sarol JN Jr., Poblete R. HIV/AIDS in the Philippines. AIDS Educ Prev 2004;16 3 Suppl A: 43-52.
20. Tupasi TE, Garfin AM, Kurbatova EV, Mangan JM, Orillaza-Chi R, Naval LC, *et al.* Factors associated with loss to follow-up during treatment for multidrug-resistant tuberculosis, the philippines, 2012-2014. Emerg Infect Dis 2016;22:491-502.
21. Li D, Wang JL, Ji BY, Cui JY, Pan XL, Fan CL, *et al.* Persistently high prevalence of primary resistance and multidrug resistance of tuberculosis in Heilongjiang Province, China. BMC Infect Dis 2016;16:516.
22. Hoagland DT, Liu J, Lee RB, Lee RE. New agents for the treatment of drug-resistant *Mycobacterium tuberculosis*. Adv Drug Deliv Rev 2016;102:55-72.
23. World Health Organization. WHO Policy on Collaborative TB/HIV

Activities: Guidelines for National Programmes and other Stakeholders. WHO Guidelines Approved by the Guidelines Review Committee: Geneva; 2012.
24. Siddiqi UR, Leano PS, Chagan-Yasutan H, Shiratori B, Saitoh H, Ashino Y, *et al.* Frequent detection of anti-tubercular-glycolipid-IgG and -IgA antibodies in healthcare workers with latent tuberculosis infection in the Philippines. Clin Dev Immunol 2012;2012:610707.
25. Kumar AM, Gupta D, Kumar A, Gupta RS, Kanchar A, Rao R, *et al.* HIV Testing among patients with presumptive tuberculosis: How do we implement in a routine programmatic setting? Results of a large operational research from India. PLoS One 2016;11:e0156487.
26. Usami O, Nakajima C, Endo S, Inomata S, Kanamori H, Hirakata Y, *et al.* A case of Manila type *Mycobacterium tuberculosis* infection in Japan. Clin Case Rep 2015;3:622-5.
27. Parwati I, van Crevel R, van Soolingen D. Possible underlying mechanisms for successful emergence of the *Mycobacterium tuberculosis* Beijing genotype strains. Lancet Infect Dis 2010;10:103-11.
28. Chagan-Yasutan H, Saitoh H, Ashino Y, Arikawa T, Hirashima M, Li S, *et al.* Persistent elevation of plasma osteopontin levels in HIV patients despite highly active antiretroviral therapy. Tohoku J Exp Med 2009;218:285-92.
29. Dembele BP, Chagan-Yasutan H, Niki T, Ashino Y, Tangpukdee N, Shinichi E, *et al.* Plasma levels of Galectin-9 reflect disease severity in malaria infection. Malar J 2016;15:403.
30. Chagan-Yasutan H, Ndhlovu LC, Lacuesta TL, Kubo T, Leano PS, Niki T, *et al.* Galectin-9 plasma levels reflect adverse hematological and immunological features in acute dengue virus infection. J Clin Virol 2013;58:635-40.
31. Anderson AC, Joller N, Kuchroo VK Lag-3, Tim-3, and TIGIT: Co-inhibitory receptors with specialized functions in immune regulation. Immunity 2016;44:989-1004.
32. Ndlovu H, Marakalala MJ. Granulomas and inflammation: Host-directed therapies for tuberculosis. Front Immunol 2016;7:434.