



COMPARISON OF TB-HIV COINFECTION STANDARDISED MORBIDITY RATES IN MALAYSIA USING DIRECT STANDARDISATION METHOD

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ABSTRACT

Tuberculosis (TB) has been the leading cause of death from an infectious disease in Malaysia for decades. It is the most common opportunistic disease among people living with HIV (PLHIV) and one-third of the HIV-related deaths were coinfecting with TB worldwide. The objective of this study was to compare the sex-, ethnicity- and age-standardised TB-HIV coinfection morbidity rates among the 13 states and three federal territories in Malaysia by using direct standardisation method. Malaysia population (as standard population) and population by state/federal territory for year 2013 and 2014 were used in the analysis. StdAn computer program was applied to calculate the sex-, ethnicity- and age-standardised morbidity rates of TB-HIV coinfection for all the populations under study. StdAn is a computer program which provides a graphically user friendly interface for the execution of standardisation analysis. The findings of the study were: (i) Based on sex-standardised morbidity rate, Kelantan had the highest risk, followed by Terengganu and Federal Territories of Kuala Lumpur/Putrajaya, whereas Federal Territory of Labuan had the lowest sex-standardised morbidity rate. (ii) Kelantan ranked the highest in ethnicity-standardised morbidity rate, followed by Federal Territories of Kuala Lumpur/Putrajaya and Pahang, while Sabah had the lowest risk. (iii) As for age factor, Kelantan scored the highest age-standardised morbidity rate, followed by Terengganu and Pahang, whereas Federal Territory of Labuan had the lowest rate. In summary, Kelantan had the highest risk of TB-HIV coinfection based on sex-, ethnicity- and age-standardised morbidity rates, whereas Federal Territory of Labuan and Sabah had the lowest risk despite having high burden of TB. Ministry of Health is suggested to focus on prevention and control of TB infection at states/federal territories which have high burden of HIV, especially the East Coast states of Peninsular Malaysia.

Keywords: TB-HIV coinfection, direct standardisation, Malaysia.

1. INTRODUCTION

Tuberculosis (TB) is a major global public health problem which ranks parallel to human immunodeficiency virus (HIV) as a leading cause of death worldwide [1]. Hence, patients who have both TB and HIV infections are more vulnerable, as each infectious agent speeds up the deterioration of patients' immune system [2]. TB is the most common opportunistic infection among people living with HIV (PLHIV), where they are 26-31 times more likely to infect with TB than people without HIV [3]. As such, HIV is known to increase the risk of latent TB reactivation and therefore causing rapid progression of TB [2, 4]. However, it remains unknown whether TB speeds up the progression of HIV infection [4].

Based on World Health Organisation (WHO) report, an estimated 1.2 million (12%) of 9.6 million people suffered from active TB were coinfecting with HIV in 2014, whereby 74% of them were from the African Region. About 0.40 million (27%) of 1.5 million people who died from TB were coinfecting with HIV [1].

In 2014, there were approximately 2.0 million new HIV cases, which resulted in 36.9 million PLHIV worldwide at the end of 2014. It was estimated 1.2 million HIV-related deaths, whereby a third of the deaths were coinfecting with TB in the same year, which made TB the leading cause of death among PLHIV [5].

Malaysia is situated in Southeast Asia, which comprises two regions that are separated by South China Sea: Peninsular Malaysia (West Malaysia) and East Malaysia. It consists of 13 states and three federal

territories with total population approximately 30 million in 2014. Malaysia is a multi-ethnic country, comprising Malay (>50%), Chinese (23%), Indian (7%), and others [6]. It is classified as a country with an intermediate burden of TB by WHO [7]. For decades, TB has been the leading cause of death from an infectious disease in Malaysia, where mortality rate of TB was 5.4 per 100,000 population in 2013. A total of 24,071 new TB cases (all forms) were reported in the same year, giving an incidence rate of 81 per 100,000 population [8].

In 2013, there were reported 3,393 new HIV infections in Malaysia, giving an incidence rate of 11.4 cases per 100,000 population [9], while 652 HIV-related deaths were recorded in the same year. It was estimated to have about 86,324 PLHIV by end of 2013 [9]. As for TB-HIV coinfection, the number reported had increased from six in 1990 to 1,477 cases in 2013 [9], which was 6.1% of new TB cases or 43.5 % of new HIV cases reported, giving an incidence rate of approximately 5 per 100,000 population.

The objective of this study was to compare the sex-, ethnicity- and age-standardised TB-HIV coinfection morbidity rates among the 13 states and three federal territories in Malaysia by using direct standardisation method.



2. MATERIALS AND METHODS

2.1 The data

Malaysia comprises 13 states (i.e. Perlis, Kedah, Penang, Perak, Selangor, Negeri Sembilan, Melaka, Johor, Kelantan, Terengganu, Pahang, Sabah and Sarawak) and three federal territories (i.e. Kuala Lumpur, Putrajaya and Labuan). The data involved in the study were from year 2013 and 2014, which were obtained from Ministry of Health, TB surveillance system (MyTB) as follows:

- Malaysia population, which was used as the standard population (Table-1).
- Population by state or federal territory in Malaysia (Table-1)
- TB-HIV coinfection by state or federal territory in Malaysia (Table-2)

Data of Federal Territories of Kuala Lumpur and Putrajaya were combined into one, same as the data source.

2.2. Direct standardisation

In epidemiology studies, populations are commonly compared on morbidity or mortality rates of a disease in order to identify populations that have higher risk [10, 11]. Due to the diverse composition of populations under study, direct comparison by using crude rate may cause confounding phenomena, where the results produced may be spurious. Therefore, standardisation analysis is applied to remove the effect of confounder, which involves a standard population that is used as a reference. There are two methods of standardisation, i.e. direct and indirect standardisation [12]. Direct standardisation is applicable when factor-specific rates of populations under study are known, else indirect standardisation is used.

In this study, direct standardisation method was applied to achieve the objective of the study. The direct standardisation procedure is shown in Figure-1 [12].

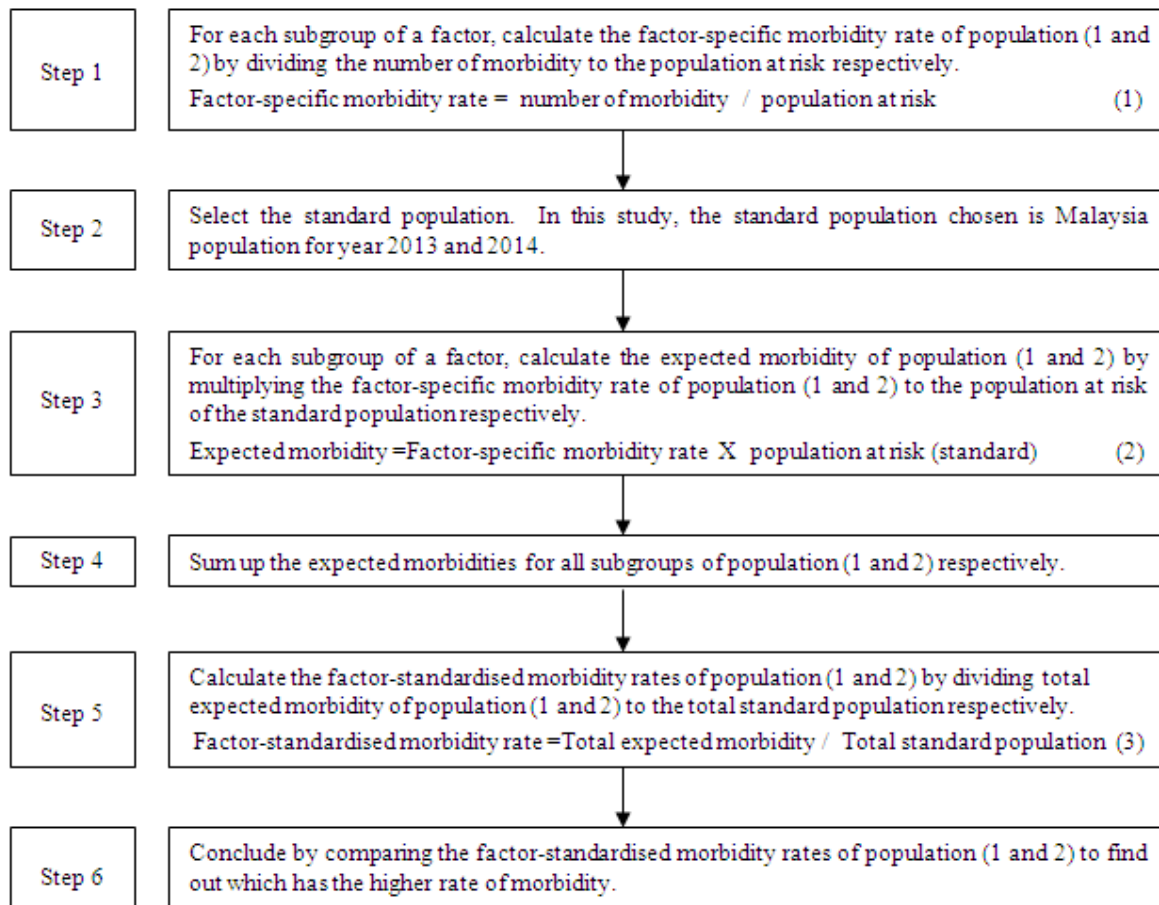


Figure-1. Flowchart showing procedures in direct standardisation method.

**Table-1.** Malaysia Population (thousands) by State or Federal Territory, 2013-2014.

Factor		State or Federal Territory															
		JHR	KDH	KLT	MLK	NS	PHG	PRK	PLS	PNG	PTJ& KL	TRG	SLG	SBH	SRW	LBN	Total
Sex	Male	3,677.4	2,052.5	1,683.3	862.8	1,110.6	1,678.3	2,471.6	239.0	1,641.5	1,851.3	1,143.7	5,961.9	3,592.2	2,680.0	97.1	30,743.2
	Female	3,315.1	2,014.8	1,674.5	852.1	1,043.6	1,492.1	2,421.5	246.0	1,632.6	1,798.9	1,101.5	5,563.5	3,321.1	2,501.0	91.3	29,069.6
	Total	6,992.5	4,067.3	3,357.8	1,714.9	2,154.2	3,170.4	4,893.1	485.0	3,274.1	3,650.2	2,245.2	11,525.4	6,913.3	5,181.0	188.4	59,812.8
Ethnicity	Malay	3,708.4	3,072.2	3,098.8	1,082.6	1,214.3	2,232.9	2,585.9	414.5	1,350.6	1,592.4	2,126.0	5,984.3	968.5	412.9	65.9	29,910.2
	Cina	2,130.6	522.5	107.6	426.5	463.4	476.6	1,418.3	38.1	1,369.1	1,353.7	54.8	2,970.6	1,407.7	330.6	21.0	13,091.1
	India	454.2	282.5	9.4	101.6	304.5	130.6	581.4	6.0	326.5	324.8	5.8	1,405.4	613.6	1,194.0	1.6	5,741.9
	Others	699.3	190.1	142.0	104.2	172.0	330.3	307.5	26.4	227.9	379.3	58.6	1,165.1	3,923.5	3,243.5	99.9	11,069.6
	Total	6,992.5	4,067.3	3,357.8	1,714.9	2,154.2	3,170.4	4,893.1	485.0	3,274.1	3,650.2	2,245.2	11,525.4	6,913.3	5,181.0	188.4	59,812.8
Age (year)	<= 24	3,031.1	1,909.3	1,807.0	773.6	972.4	1,530.9	2,171.9	234.9	1,263.9	1,399.1	1,183.8	4,709.7	3,387.7	2,382.1	89.1	26,846.5
	25-34	1,277.9	599.6	421.4	286.7	357.5	538.7	698.5	70.7	599.1	804.5	335.9	2,601.9	1,470.1	852.9	42.0	10,957.4
	35-44	959.9	494.5	345.0	203.7	263.1	364.7	564.3	48.9	485.0	546.8	239.6	1,769.2	880.7	671.4	23.6	7,860.4
	45-54	784.7	461.5	342.7	194.6	237.5	322.4	573.9	53.8	396.5	436.0	221.7	1,233.6	622.7	572.4	18.7	6,472.7
	>= 55	938.9	602.4	441.7	256.3	323.7	413.7	884.5	76.7	529.6	463.8	264.2	1,211.0	552.1	702.2	15.0	7,675.8
	Total	6,992.5	4,067.3	3,357.8	1,714.9	2,154.2	3,170.4	4,893.1	485.0	3,274.1	3,650.2	2,245.2	11,525.4	6,913.3	5,181.0	188.4	59,812.8

Source: Ministry of Health, TB surveillance data 2015.

Note: JHR- Johor, KDH- Kedah, KLT- Kelantan, MLK- Melaka, NS- Negeri Sembilan, PHG- Pahang, PRK- Perak, PLS- Perlis, PNG- Penang, PTJ- Federal Territory of Putrajaya, KL- Federal Territory of Kuala Lumpur, TRG- Terengganu, SLG- Selangor, SBH- Sabah, SRW- Sarawak, LBN- Federal Territory of Labuan.

Table-2. TB-HIV Coinfection by State or Federal Territory in Malaysia, 2013-2014.

Factor		State or Federal Territory															
		JHR	KDH	KLT	MLK	NS	PHG	PRK	PLS	PNG	PTJ& KL	TRG	SLG	SBH	SRW	LBN	Total
Sex	Male	287	101	313	71	94	203	122	12	92	215	173	430	114	86	2	2,315
	Female	29	21	38	10	11	26	22	5	17	43	21	56	34	26	1	360
	Total	316	122	351	81	105	229	144	17	109	258	194	486	148	112	3	2,675
Ethnicity	Malay	224	85	335	71	80	198	75	12	41	116	191	263	3	17	2	1,713
	Cina	60	15	9	5	10	13	27	1	35	58	1	83	29	19	0	365
	India	24	17	0	3	10	6	34	0	22	33	0	70	0	1	0	220
	Others	8	5	7	2	5	12	8	4	11	51	2	70	116	75	1	377
	Total	316	122	351	81	105	229	144	17	109	258	194	486	148	112	3	2,675
Age (year)	<= 24	10	3	7	4	4	7	4	2	3	13	6	19	12	12	0	106
	25-34	68	34	98	17	28	68	40	3	23	76	50	152	57	33	2	749
	35-44	143	39	194	42	42	106	60	8	40	91	105	189	34	41	1	1,135
	45-54	71	36	41	17	20	39	28	4	27	58	28	94	24	15	0	502
	>= 55	24	10	11	1	11	9	12	0	16	20	5	32	21	11	0	183
	Total	316	122	351	81	105	229	144	17	109	258	194	486	148	112	3	2,675
Crude morbidity rate (per 100K population)		4.52	3.00	10.45	4.72	4.87	7.22	2.94	3.51	3.33	7.07	8.64	4.22	2.14	2.16	1.59	4.47

Source: Ministry of Health, TB surveillance data 2015.

Note: JHR- Johor, KDH- Kedah, KLT- Kelantan, MLK- Melaka, NS- Negeri Sembilan, PHG- Pahang, PRK- Perak, PLS- Perlis, PNG- Penang, PTJ- Federal Territory of Putrajaya, KL- Federal Territory of Kuala Lumpur, TRG- Terengganu, SLG- Selangor, SBH- Sabah, SRW- Sarawak, LBN- Federal Territory of Labuan.



SRW- Sarawak, LBN- Federal Territory of Labuan.

2.3. Statistical analysis

StdAn computer program was used to calculate the sex-, ethnicity- and age-standardised morbidity rates for all the populations involved in the study. StdAn is a computer program developed by using Windows Forms application in Microsoft Visual C++ 2010 Express software. Its graphically easy-to-use interface enables the implementation of standardisation analysis in shorter time and at cheaper cost. It can be downloaded free of charge at www.medic.usm.my/biostat/ or by sending your request via email to wnarifin@usm.my.

3. RESULTS

3.1 TB-HIV Coinfection in Malaysia

The study showed that Malaysia TB-HIV crude morbidity rate for the study duration was 4.47 per 100,000 population. Table-3 displays TB-HIV factor-specific morbidity rates of the country, whereby, the sex-specific morbidity rate for males was higher than females, i.e. 7.53 per 100,000 population and 1.24 per 100,000 population, respectively.

Based on ethnicity-specific morbidity rates, Malay was identified to have the highest risk as compared to other ethnicities in the country, i.e. 5.73 per 100,000 population. Followed by Indian and Chinese, with 3.83 and 2.79 per 100,000 population respectively.

The TB-HIV age-specific morbidity rate was the lowest for people under the age of 25 (0.39 per 100,000 population) and was at its peak between 35 to 44 years old (14.44 per 100,000 population) before decreasing after the age of 44.

Table-3. TB-HIV Factor-specific morbidity rate (per 100,000 population) in Malaysia, 2013-2014.

Factor		TB-HIV Coinfection	Malaysia Population ('000)	Factor-specific morbidity rate (per 100,000 population)
Sex	Male	2,315	30,743.2	7.53
	Female	360	29,069.6	1.24
	Total	2,675	59,812.8	4.47
Ethnicity	Malay	1,713	29,910.2	5.73
	Cina	365	13,091.1	2.79
	India	220	5,741.9	3.83
	Others	377	11,069.6	3.41
	Total	2,675	59,812.8	4.47
Age (year)	<= 24	106	26,846.5	0.39
	25-34	749	10,957.4	6.84
	35-44	1,135	7,860.4	14.44
	45-54	502	6,472.7	7.76
	>= 55	183	7,675.8	2.38
	Total	2,675	59,812.8	4.47

Source:Ministry of Health, TB surveillance data 2015.

3.2 TB-HIV coinfection among states and federal territories in Malaysia

Based on TB-HIV crude morbidity rates among states and federal territories in Malaysia (Table-2), Kelantan scored the highest (10.45 per 100,000 population) and Federal Territory of Labuan recorded the lowest (1.59 per 100,000 population) rate.

The results of the sex-, ethnicity- and age-standardised morbidity rates of TB-HIV coinfection are displayed in Table-4.

3.2.1 Sex-standardised morbidity rate

Comparing the sex-standardised morbidity rate among the states and federal territories in Malaysia, Kelantan had the highest risk (10.66 per 100,000 population), followed by Terengganu (8.70 per 100,000 population) and Federal Territories of Kuala Lumpur/Putrajaya (7.13 per 100,000 population). On the other hand, Federal Territory of Labuan had the lowest risk, where the sex-standardised morbidity rate was 1.59 per 100,000 population.



3.2.2 Ethnicity-standardised morbidity rate

Kelantan was also ranked the highest in ethnicity-standardised morbidity rate (8.15 per 100,000 population), followed by Federal Territories of Kuala Lumpur/Putrajaya (8.04 per 100,000 population) and Pahang (6.15 per 100,000 population). On the contrary, Sabah had the lowest risk based on ethnicity-standardised morbidity rate, i.e. 1.15 per 100,000 population.

3.2.3 Age-standardised morbidity rate

As for age standardisation, Kelantan had the highest age-standardised morbidity rate (13.44 per 100,000 population), followed by Terengganu (10.32 per 100,000 population) and Pahang (7.93 per 100,000 population), while Federal Territory of Labuan had the lowest age-standardised morbidity rate, 1.43 per 100,000 population.

Table-4. Direct standardisation: TB-HIV factor-standardised morbidity rate (per 100,000 population) by State or Federal Territory in Malaysia, 2013-2014.

Factor	State or Federal Territory														
	JHR	KDH	KLT	MLK	NS	PHG	PRK	PLS	PNG	PTJ&KL	TRG	SLG	SBH	SRW	LBN
Sex	4.437	3.036	10.660	4.800	4.863	7.064	2.979	3.569	3.387	7.131	8.701	4.196	2.129	2.160	1.591
Ethnicity	4.356	3.076	8.149	4.180	4.620	6.150	2.910	4.826	3.618	8.044	5.524	4.399	1.153	3.753	1.703
Age	4.388	3.203	13.438	5.023	5.070	7.926	3.231	4.114	3.018	6.328	10.323	3.819	2.282	2.222	1.429

Source: Ministry of Health, TB surveillance data 2015.

Note: JHR- Johor, KDH- Kedah, KLT- Kelantan, MLK- Melaka, NS- Negeri Sembilan, PHG- Pahang, PRK- Perak, PLS- Perlis, PNG- Penang, PTJ- Federal Territory of Putrajaya, KL- Federal Territory of Kuala Lumpur, TRG- Terengganu, SLG- Selangor, SBH- Sabah, SRW- Sarawak, LBN- Federal Territory of Labuan.

4. DISCUSSIONS

East Malaysia which consists of Sabah, Sarawak and Federal Territory of Labuan, contributed around 30% of Malaysia new TB cases in 2013. TB control remains a great challenge in East Malaysia, especially Sabah which had the highest number of TB cases among the states/federal territories in Malaysia, contributing approximately 20% of the total new TB cases of the country, with an incidence rate of 132.0 per 100,000 population in 2013 [13, 14]. Both Sarawak and Federal Territory of Labuan had high TB incidence rate too, i.e. slightly above 100 per 100,000 population, far exceeded the national incidence rate of 81 per 100,000 population in 2013 [8]. Despite having high burden of TB in East Malaysia, the results of this study indicated that its sex-, ethnicity- and age-standardised TB-HIV coinfection morbidity rates were among the lowest in the country.

Kelantan, on the other hand, was among the states with the highest number of new HIV cases in the country [15, 16]. The national surveillance system had reported a cumulative of 101,672 HIV cases from 1986 to 2013, where Kelantan ranked the third highest number of HIV cases (contributing around 11%) after Johor and Selangor [17]. And, in this study, Kelantan was concluded as the riskiest state of TB-HIV coinfection based on sex-, ethnicity- and age-standardised TB-HIV coinfection morbidity rates.

The limitation of this study is the surveillance data used in this study were not the final data for the study duration. Nevertheless, it had enabled us to achieve the study objective.

5. CONCLUSIONS

Kelantan which was known of high burden of HIV was also found to have the highest risk of TB-HIV coinfection based on sex-, ethnicity- and age-standardised morbidity rates, whereas Federal Territory of Labuan and Sabah had the lowest risk among the 13 states and three federal territories in Malaysia, even though they have high burden of TB. This study had shown that HIV accelerates TB infection; on the other hand, TB infection may not be the significant factor to contain HIV infection. In order to control TB-HIV coinfection, Ministry of Health is recommended to focus on prevention and control of TB infection at states/federal territories which have high HIV burden, especially the East Coast states of Peninsular Malaysia.

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REFERENCES

- [1] 2015. WHO, Global tuberculosis report 2015.
- [2] Pawlowski A., *et al.* 2012. Tuberculosis and HIV co-infection. *PLoSPathog.* 8(2): e1002464.



- [3] WHO. TB/HIV. 2015 [accessed Feb 20, 2016]; Available from: <http://www.who.int/tb/challenges/hiv/en/>.
- [4] Kwan C.K. and J.D. Ernst. 2011. HIV and tuberculosis: a deadly human syndemic. *Clinical microbiology reviews*. 24(2): 351-376.
- [5] WHO. HIV/AIDS Fact Sheets. 2015 [accessed Feb 18, 2016]; Available from: <http://www.who.int/mediacentre/factsheets/fs360/en/>.
- [6] 2015. MOH (Malaysia), The Global AIDS Response Progress Report 2015: Malaysia, in Country Progress Report.
- [7] Rafiza S., K.G. Rampal and A. Tahir. 2011. Prevalence and risk factors of latent tuberculosis infection among health care workers in Malaysia. *BMC infectious diseases*. 11(1): 1.
- [8] MOH (Malaysia). The ninth Technical Advisory Group and National TB Programme Managers meeting for TB control in the Western Pacific Region. Country Progress Report: Malaysia. 2014 [accessed Feb 10, 2016]; Available from: www.wpro.who.int/tb/meetings/4_4_mys.ppt.
- [9] 2014. MOH (Malaysia), The Global AIDS Response Progress Report 2014: Malaysia, in Country Progress Report.
- [10] França E., *et al.* 2012. Comparison of crude and adjusted mortality rates from leading causes of death in northeastern Brazil. *Revista Panamericana de Salud Pública*. 31(4): 275-282.
- [11] Thorsen K., *et al.* 2013. Epidemiology of perforated peptic ulcer: age-and gender-adjusted analysis of incidence and mortality. *World J Gastroenterol*. 19(3): 347-54.
- [12] Naing N.N. 2000. Easy way to learn standardization: direct and indirect methods. *The Malaysian journal of medical sciences: MJMS*. 7(1): 10-15.
- [13] William T., *et al.* 2015. Pulmonary tuberculosis in outpatients in Sabah, Malaysia: advanced disease but low incidence of HIV co-infection. *BMC Infectious Diseases*. 15: 32-32.
- [14] Rashid Ali, M.R.S., *et al.* 2015. A prospective study of tuberculosis drug susceptibility in Sabah, Malaysia, and an algorithm for management of isoniazid resistance. *Journal of tropical medicine*.
- [15] Ariffin T.A.A.T.M., *et al.* 2014. Antiretroviral drug resistance and HIV-1 subtypes among treatment-naive prisoners in Kelantan, Malaysia. *The Journal of Infection in Developing Countries*. 8(08): 1063-1067.
- [16] Mohamad S., *et al.* 2012. Assessing subtypes and drug resistance mutations among HIV-1 infected children who failed antiretroviral therapy in Kelantan, Malaysia. *Brazilian Journal of Infectious Diseases*. 16(3): 284-288.
- [17] UNAIDS. HIV and AIDS Data Hub for Asia-Pacific, Review in slides: Malaysia. 2016 [accessed Feb 15, 2016]; Available from: <http://aidsdatahub.org/Country-Reviews>.