

## The stages of HIV infection and the risk of opportunistic Tuberculosis infection

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### Abstrak

**Latar belakang:** Infeksi oportunistik (IO) oleh tuberkulosis adalah penyebab kematian tertinggi orang yang terinfeksi HIV di seluruh dunia, terutama pada infeksi HIV yang tidak diobati. Tujuan penelitian ini adalah untuk mengetahui faktor risiko infeksi oportunistik TB pada orang dengan HIV.

**Metode:** Studi dilakukan di klinik konseling sukarela (VCT) di beberapa rumah sakit di tujuh provinsi (Sumatera Utara, Sumatera Barat, Kepulauan Riau, Sulawesi Selatan, Sulawesi Utara, Maluku, dan Papua). Desain penelitian adalah potong lintang dan pemilihan responden dengan metode purposive sampling. Sebanyak 490 pasien HIV dimasukkan dalam penelitian ini. Data dikumpulkan dengan menggunakan kuesioner yang spesifik. Analisis statistik dilakukan menggunakan STATA versi 9.0.

**Hasil:** Di antara 490 pasien HIV, 238 (48,6%) pasien melaporkan TB sebagai IO. Semakin muda kelompok subyek dengan HIV semakin besar persentase IO TB. Penderita HIV laki-laki mempunyai risiko 24% lebih tinggi terinfeksi TB dibandingkan perempuan [risiko relatif suaian (RRa) = 1,24; P = 0,023]. Sedangkan subyek dengan tingkat stadium 1 sampai dengan 3 dibandingkan subyek dengan tingkat stadium akhir berisiko 52% terinfeksi TB (RRa = 1,55; P = 0,000).

**Kesimpulan:** Infeksi HIV stadium 4 dan penderita laki-laki lebih berisiko terkena IO TB. (*Health Science Journal of Indonesia 2015;6:121-5*)

**Kata kunci:** Tuberkulosis, HIV, infeksi oportunistik, Indonesia

### Abstract

**Background:** Opportunistic infection (OI) by tuberculosis is the most common cause of death for people infected with HIV worldwide, mainly in persons with untreated HIV infection. The aim of the study was to determine the risk factors associated with TB as an OI of HIV-infected patients.

**Methods:** The study conducted in Voluntary Counseling Testing (VCT) clinics in several hospitals of seven provinces (North Sumatera, West Sumatera, Riau Islands, South Sulawesi, North Sulawesi, Maluku, and Papua). This was a cross sectional study and the respondents selected by purposive sampling. There were 490 HIV patients included in this study. Data were collected using a specific questionnaire. Statistical analyses were done using STATA 9.0 version.

**Results:** Among 490 HIV patients, there were 238 (48.6%) patients with TB as IO. The percentage of TB as OI in the younger HIV-infected group was higher than the older group. Among the HIV-infected persons, males had a 24 % higher risk of becoming infected with TB than females [adjusted relative risk (RRa)=1.24; P=0.023]. Stage 4 HIV-infected persons had 52% risk of TB as OI compared to stages 1-3 (RRa=1.55; P=0.000).

**Conclusion:** Patients with stage 4 HIV infection and male were more at risk for developing opportunistic tuberculosis infection. (*Health Science Journal of Indonesia 2015;6:121-5*)

**Keywords:** Tuberculosis, HIV, opportunistic infection, Indonesia

Indonesia has the 4<sup>th</sup> highest number patients with Tuberculosis in the world. Tuberculosis or TB is an infection caused by *Mycobacterium tuberculosis* and has been recognized a long time ago, especially in developing countries such as Indonesia. At the beginning of infection, tuberculosis may cause no symptoms. People infected with HIV are more likely than others to become sick with TB. HIV infection will significantly increase the risk of progression from latent to active TB disease. This risk can be expected to be different if infection occurs in an HIV-negative person, where more than 90% will not develop into active TB disease. Active TB will occur more rapidly in HIV cases with approximately 50% probability to develop into active TB disease. Detection of TB in people with HIV disease is more difficult.<sup>1</sup>

The World Health Organization reported in 2013, that around 9 million people developed TB and 1.5 million will die. Among the 1.5 million deaths from TB, 360,000 had HIV. The report also stated that 320,000 of the 1.3 million people with tuberculosis who died were people with HIV-AIDS.<sup>2</sup> TB negatively impacts the natural history of HIV infection. The opportunistic infection (OI) by tuberculosis is the most common cause of death for people infected with HIV worldwide, mainly in persons with untreated HIV disease. Once people get infected with HIV, the immune system will weaken and lead to the development of TB rapidly.<sup>3,4</sup>

Several studies found that the prevalence of HIV among new TB cases in several provinces was varied. In 2006, the prevalence of HIV among new TB cases was 2% in Yogyakarta province. In 2008, the prevalence in East Java, Bali, and Papua were 0.8%, 3.8%, and 14% respectively. In Indonesia, TB infection was a challenge for AIDS control since TB is the most infectious disease that infects people with HIV-AIDS (31.8%). In 2013, WHO estimated the number TB patients with HIV positive in Indonesia was 7.5%, this number has increased from 3.3% in 2012.<sup>5</sup>

Most of the data on TB related to HIV came from HIV control programs, therefore it was important to analyze the risk factors of TB infection among HIV patients. The aim of this study was to determine the risk factors of TB as OI among HIV patients in seven provinces in Indonesia in 2007.

## METHODS

This study is a part of HIV/AIDS cross-sectional study in seven provinces in Indonesia in 2011. The subjects consisted of HIV/AIDS cases visited by

the Voluntary Counseling Testing (VCT) clinics in purposive selected from seven provinces in Indonesia (North Sumatera, West Sumatera, Riau islands, South Sulawesi, North Sulawesi, Maluku, and Papua). In each province, 1 or 2 hospitals were selected purposively.

The subjects consisted of confirmed positive HIV/AIDS using 3 rapid test by different methods or 2 rapid tests by different methods and 1 timed test by ELISA method. Severe cases were excluded.

The subjects were also selected by purposive sampling. There were 490 HIV-AIDS infected patients included in this study. Interviewers and data collection lasted 1 week and carried out by the team from Center for Biomedical and Basic Technology of Health, National Institute of Health Research and Development, Ministry of Health Republic of Indonesia.

The data were obtained by interview using a structured questionnaire. Data were analyzed to obtain the percentage of the variables studied.

This analysis used a part of HIV/AIDS cross sectional study in seven provinces in Indonesia in 2011. The subjects consisted of HIV/AIDS cases visited Volunteer Care and Treatment (VCT) clinics in purposive selected seven provinces (North Sumatera, West Sumatera, Riau islands, South Sulawesi, North Sulawesi, Maluku, and Papua). For each province was selected 1 or 2 hospitals purposively.

The subjects consisted of confirmed positive HIV/AIDS using 3 rapid test by different methods or 2 rapid tests by different and 1 time test by ELISA method in participating. We excluded severe cases.

The selection of the subjects by purposive sampling method. There were 490 HIV- infected persons included in this study. Interviewers and data collection for 1 week by researcher's personnel of the Center for Biomedical and Basic Health Technology.

The data was obtained by interview using a structured questionnaire and analyzed to obtain a percentage of the variables studied.

All of the HIV-infected persons asked for the Opportunistic infection (TB OI) during the HIV infections. Especially for TB as OI, they had to inform how the diagnosis have been enforced such as the laboratory confirm or Rontgen. The subjects were asked about the TB medication. Interviewers and data collection for 1 week by researcher of the Center for Biomedical and Basic Health Technology.

The logistic regression method were done using STATA 9.0 version to identify the dominant risk factors related to TB OI.

This study received ethical clearance from the Ethical Committee of the Litbangkes, and informed consent available from the subjects.

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## RESULTS

All of the 490 patients were analyzed. Table 1 showed that the proportion of active tuberculosis OI in HIV infected subjects was 48.6%. In terms of gender, the number of HIV-infected persons was higher in men

compared to women (53%). While the proportion of tuberculosis OI was greater in the younger age group (64%). It appeared that active TB developed very rapidly in HIV-positive cases.

Table 1 showed that persons who had and did not have opportunistic TB infection were similarly distributed in terms of age and persons with CD4 counts.

HIV-infected persons residing in the Papua province had the highest risk for opportunistic TB infection which was equal to 117% compared to those living in the province of North Sumatera. The risk for opportunistic TB infections among six other provinces was lowest in West Sumatra province or 13% compared to those who live in North Sumatera

Tabel 2, the final model, gender and the stage of HIV infection were the dominant risk factors for OI TB. In terms of gender, male had a 24% higher risk for OI TB. Furthermore stage 4 HIV cases had a 52% higher risk for OI TB compared with stages 1-3 of the HIV infection.

Table 1. Several demographic, clinical characteristic and the risk of opportunistic TB infection

	Opportunistic TB infection				Crude relative risk	95% confidence interval	P
	No (n=252)		Yes (n=238)				
	n	%	n	%			
Age							
0-14 years	5	35.7	9	64.3	1.00	Reference	
15-30 years	95	48.5	101	51.5	0.80	0.40-1.58	0.525
31-65 years	152	54.3	128	45.7	0.71	0.36-1.39	0.323
Province							
North-Sumatera	47	67.1	23	32,9	1.00	Reference	
West-Sumatera	44	62.9	26	37,1	1.13	0.64-1.98	0.668
Riau Island	42	60.0	28	40,0	1.21	0.70-2.11	0.485
South-Sulawesi	34	48.6	36	51,4	1.56	0.92-2.64	0.093
North-Sulawesi	33	47.1	37	52,9	1.60	0.95-2.70	0.073
Maluku	32	45.7	38	54,3	1.65	0.98-2.77	0.057
Papua	20	28.6	50	71.4	2.17	1.32-3.56	0.002
CD4 count							
351-1523/mm3	74	56.5	57	43.5	1.00	Reference	
0-350/ mm3	178	49.6	181	50.4	1.15	0.86-1.56	0.332

Table 2. The relationship between gender, stage of HIV and risk of opportunistic TB infection

	Opportunistic infection TB				Adjusted relative risk	95% confidence interval	P
	No (n=252)		Yes (n=238)				
	n	%	n	%			
Gender							
Female	126	58.1	91	41.9	1.00	Reference	-
Male	126	46.1	147	53.9	1.24	1.03-1.50	0.023
Stage							
Stage 1-3	233	54.8	192	45.2	1.00	Reference	-
Stage 4	19	29.2	46	70.8	1.52	1.25-1.84	0.000

## DISCUSSIONS

The limitation of this study was that CD4 count of < 200 cells/uL was not analyzed. A study conducted by Masur *et al*, reported that HIV-infected persons with CD4 count of < 200 cells/uL were easily infected with the bacteria that caused pneumonia, such as *Mycobacterium Avium-intracellulare*.<sup>11</sup>

Treatment to improve quality of life and prolong life in people with HIV is currently booming and is progressively getting better. However, infectious complications still remains a threat to people with HIV. Most complications causing hospitalization of people with HIV are pulmonary complications (30-40 %). Several previous studies mentioned that the main cause of lung infection complications is caused by *P. carinii*, followed by Tuberculosis.<sup>9</sup> Currently, the major complication based on the results of this study showed Tuberculosis.

This study showed that the increase of active TB is proportionately parallel to the severity of HIV. This finding corresponded to those reported by other studies, which showed that the OI TB developed actively among HIV-positive cases especially with those with lower CD4 counts. The risk of progressing from latent to active TB is estimated to be between 12 and 20 times greater in people living with HIV than among those without HIV infection.<sup>8</sup> The best way to prevent the OI TB was by avoiding exposure of HIV-infected persons to TB. This was rather difficult since TB is endemic in Indonesia.<sup>8</sup> Knowing the early presence of TB infection in people with HIV is to do a tuberculin skin test (TST) using 5-TU purified protein derivative (PPD) by the Mantoux method (AI) at the time the person is diagnosed with HIV. If the result is a positive TST ( $\geq 5$  mm of induration), then a chest x-ray should be done immediately and treatment started for active TB. All people with HIV and a positive TST result, even without any symptoms of active TB or TB treatment history, should be as latent TB.<sup>10</sup>

Generally, the symptoms of pulmonary tuberculosis in HIV-infected persons have no symptoms if the CD4 count is > 350 cells/mL. But if CD4 count is down to 50 cells/uL, it will be accompanied by extrapulmonary TB.<sup>9</sup> In this study, it appeared that HIV-infected persons with CD4 < 350 cells/mL was at a higher risk for TB infection compared to HIV-infected persons with CD4 > 350 cells/uL.

In stages 1 and 2 of positive HIV cases, there were no TB infection reported. This was probably due to the

lack of chest x-rays done among HIV 1 and 2 stages, since no TB symptoms were present. The majority (76%) cases of active TB in HIV-positive patients had more than one types of OI. The risk of HIV-infected persons developing TB infection is higher since HIV and TB are closely related. Globally, 50% of HIV-infected persons developing TB. The development of TB among HIV-infected persons is related to immunosuppression. The risk was increased with the increasing degree of the immunosuppression.<sup>12</sup> In this study, the same pattern was found, where stage 4 of HIV-infected persons with immunosuppression have higher risk to develop TB infection than those without immunosuppression.

In conclusion, patients with stage 4 of HIV infection and males were more at risk for developing TB IO. Therefore for early detection of TB should be a concern. Opportunistic infection can occur at the different stages of HIV infections. The incidence of TB as the OI among HIV patients in Indonesia were high and it is very important to test for TB in every HIV patients.

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