Effect of isoniazid preventive therapy on tuberculosis incidence in people living with HIV-AIDS at Hasan Sadikin hospital

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Abstract. Indonesia is the second largest number of tuberculosis (TB) in the world. Isoniazid Preventive Therapy (IPT) as one of the three I’s TB-HIV collaboration to manage TB in people living with HIV / AIDS (PLHIV) has not been fully performed. It is related to doubt to get rid of TB in PLHIV. This study aims to see the effect of IPT on the incidence of TB in PLHIV. This issue is a retrospective cohort study based on medical record data in HIV clinic. Inclusion criteria are PLHIV ≥ 15 years of age who were registered to visit the CST service and obtain IPT with good adherence if they were receiving ART. Of 462 patients, HIV-infected patients receiving IPT were 154 (33.3%). IPT administration has a protective effect on PLHIV where the rate of TB incidence in PLHIV who received IPT were 0.21 times lower than those who did not receive IPT (IRR = 0.21, 95% CI 0.023-0.881, p 0.008). In this population, IPT administration reduces 79% risk of PLHIV to suffer TB. IPT administration reduces the incidence of TB.

1. Introduction

Tuberculosis (TB) and Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) are public health threat.[1] Among HIV infected patients, TB is the most frequent life-threatening opportunistic disease, even in those receiving Highly Active Antiretroviral Therapy (HAART) and it has been shown to be a leading cause of death.[2] HIV infection is also the potential risk factor for TB disease.[3] PLHIV (people living with the human immunodeficiency virus) are at least 26 times more likely to develop TB disease than people without HIV.[1]

The number of TB cases in Indonesia according to WHO report the year 2015, an estimated 1 million new TB cases per year (399 per 100,000 inhabitants) with 100,000 deaths per year (41 per 100,000 inhabitants). An estimated 63,000 cases of TB are HIV positive (25 per 100,000 population). Case Notification Number Rate/CNR of all cases, reported as many as 129 per 100,000 population. The total number is 324,539 cases, among them 314,965 is a new case. Nationally estimates HIV prevalence among tuberculosis patients is estimated at 6.2%.[4] The World Health Organization (WHO) recommended a package of collaborative TB-HIV activities in 2004.[1]

One of the pillars, to reduce the burden of TB among PLHIV, involves the Three I's approach of intensified case finding (ICF), isoniazid preventive therapy (IPT) and TB infection control (IC), in addition to early antiretroviral therapy (ART). ICF involves regular screening of all PLHIV for active...
TB disease and the provision of anti-tuberculosis treatment for active disease. IPT treats tuberculous infection and can reduce progression to active TB by 32–62% for up to 48 months.[1] Since 1998, WHO and the Joint United Nations Program on HIV/AIDS (UNAIDS) have recommended Isoniazid Preventive Therapy (IPT) as one of the key interventions in the comprehensive HIV/AIDS care strategy to reduce the burden of TB among HIV infected patients.[5] According to WHO, IPT given to HIV infected patients without TB disease reduces the risk of developing TB by 33–67%. Regarding the concomitant use of HAART with IPT, a meta-analysis led by WHO found out that HAART reduces the individual risk of TB disease by 65%, irrespective of the CD4 cell count. Recent evidence has shown that the combined use of IPT and HAART among HIV infected patients significantly reduces the incidence of TB by up to 97%.[1] However, the effectiveness of IPT in reducing the burden of active TB among HIV infected patients has not been fully performed. It is related to doubt to get rid of TB in PLHIV. Therefore, this study aims to see the effect of IPT on the incidence of TB in PLHIV in HIV clinic.

2. Methods
This study is a retrospective cohort study based on medical record data in RSHS Teratai clinic from May 2012 to May 2016. Inclusion criteria are PLHIV ≥ 15 years of age who were registered to visit the CST service and obtain IPT with good adherence if they were receiving ART. The control group is PLHIV who did not get IPT. In the control group, systemic random sampling was found by matching by sex, history of TB status, duration of HIV status.

The baseline data includes age, gender, educational background, marital status, occupation, history of tuberculosis, duration of HIV status. The outcome assessed is the incidence of tuberculosis or not. To fulfill multivariate analysis, the sample estimate used for this research is 456 samples. A significant level was set at 0.05. Duration of observation is set for 12-48 months. Data processing research using device STATA ver 12.0. Descriptive analysis includes distribution in each group and incidence of cumulative TB. Chi-square bivariate analysis was used to assess incidence rate ratio of independent variables and risk factors associated with TB incidence.

3. Results
Sampling was conducted in 2 steps, in the control group performed by systemic random sampling by matching by sex, history of TB status, and duration of HIV status in the group exposed sequentially. In Table 1, as many as 462 patients were analyzed there were 154 (33.3%) PLHIV who received IPT, and those who did not get IPT are 308 (66.7%) of PLHIV. Of the 462 dependent variable distribution samples, 20 (4.3%) PLHIV had TB and 442 (95.7%) PLHIV had no TB. Based on the variables of social demographic characteristics, age domination was 26-45 years (91.8%), the gender of most males (66.9%), education dominated by high school graduates (50.2%), married (54%), and have a job (65%).

Based on clinical characteristics most of them (69.9%) had no history of tuberculosis, 36.6% were in HIV stage III, duration of HIV status>5 years was 53.5%, more than half (56.7%) was CD4 <350 / mm3 and as many as 95.5% had received ART.

Incidence Rate Ratio (IRR) of TB in PLHIV that received IPT and not received IPT is in Table 2. Incidence rate in PLHIV that get IPT is 0.5 cases/100P-PY (95% CI 0.0126-2.027, p 0.008). In PLHIV who did not get IPT, the incidence rate of tuberculosis cases increased significantly 4.8 times that is 2.4 cases/100P-PY (95% CI 1.515-3.816). The conclusion is the IPT gives a significant protective effect on PLHWA. The incidence rate of tuberculosis in PLHIV that got IPT 0.21 times (IRR-0.21, 95% CI 0.023-0.881, p 0.008) was lower than that of PLHIV who did not get IPT. Granting IPT reduced 79% PLHIV rate in TB incidence (95% CI 0.023-0.881, p 0.08).
Table 1. Frequency distribution of independent variable, dependent variable and covariate variable at PLHIV in RSHS, during May 2012-May 2016.

| Research Variable | Category             | Frequency | %   |
|-------------------|----------------------|-----------|-----|
| **Independent Variable** |                       |           |     |
| IPT status         | Get IPT              | 154       | 33.3|
|                    | Not getting IPT      | 308       | 66.7|
| **Dependent variable** |                       |           |     |
| TB incidence       | TB                   | 20        | 4.3 |
|                    | No TB                | 442       | 95.7|
| **Social demographic variable** |               |           |     |
| Age                | 15-25 years old      | 16        | 3.5 |
|                    | 26-35 years old      | 220       | 47.6|
|                    | 36-45 years old      | 204       | 44.2|
|                    | >45 years old        | 22        | 4.7 |
| Gender             | Man                  | 309       | 66.9|
|                    | Women                | 153       | 33.1|
| Educational background | College             | 175       | 37.9|
|                    | High school          | 232       | 50.2|
|                    | Junior high school   | 44        | 9.5 |
|                    | Elementary school    | 11        | 2.4 |
| Marital status     | Married              | 155       | 33.1|
|                    | Not married          | 243       | 53.9|
|                    | Widow/doubt          | 60        | 13  |
| Occupation         | Job                  | 301       | 65.2|
|                    | Jobless              | 161       | 34.8|
| Clinical variables | History of TB        |           |     |
|                    | No                   | 323       | 69.9|
|                    | Yes                  | 139       | 30.1|
| HIV stage          | I                    | 102       | 22.1|
|                    | II                   | 35        | 7.5 |
|                    | III                  | 169       | 36.6|
|                    | IV                   | 156       | 33.8|
| Duration of HIV    | 1-2 years            | 91        | 19.7|
|                    | 3-5 years            | 124       | 26.8|
|                    | > 5 years            | 247       | 53.5|
| CD4 count          | >350/mm3             | 200       | 43.3|
|                    | <350/mm3             | 262       | 56.7|
| ART status         | Not getting ART      | 21        | 4.5 |
|                    | Get ART              | 441       | 95.5|
Table 2. Incidence rate ratio of tuberculosis incidence in PLHIV who received IPT and non-exposed IPT.

| IPT status | TBC | IR (per 100P-PY) | P-value |
|------------|-----|-----------------|---------|
| Yes        | 2   | 0.5 (0.126-2.027) | 0.008   |
| No         | 18  | 2.4 (1.515-3.816) |         |

4. Discussion
This retrospective cohort study takes from 2012 to May 2016 attempted to assess the effectiveness of IPT against the incidence of TB in PLHIV. Accordingly, the IRR were (IRR 0.21, 95% CI 0.023-0.881, p 0.008) in PLHIV who get IPT, the IRR among IPT treatment was lower when compared with the findings of studies done in different countries.[6] The recent study among patients who completed IPT, though TB had occurred after six months, almost 50% of them developed TB at 19th month, while in IPT non-exposed patients, half of the patients developed active TB within a month time. The study showed that IPT had been significantly protecting early occurrence of TB during the first six months. This finding was comparable to the study done in Thailand where IR among IPT completers was 0 and among non-exposed patients 8.60/100 P-Y.[7] Moreover, the present study indicated that IPT had offered a significant protective effect until three years. The durability of protective effect of IPT documented in the present study concurs with the expected level indicated in Ethiopian guideline.[8]

In bivariate analysis related to IPT in TB incidence, it was found that IPT in PLHWA had a significant protective effect, where the incidence of TB incidence in PLHIV was 0.21 times (IRR 0.21, 95% CI 0.023-0.881, p 0.008) lower than non exposed patients. So in this study, IPT decreased TB incidence rate by 79%. This research supported the previous research done in Rwanda, that the incidence rate of TB in PLHWA was 0.27 (IRR 0.273, 95% CI 0.152-0.493, p <0.001) lower than non-exposed patient.

5. Conclusion
Implementation of IPT in PLHIV gives a protective effect significantly after being controlled with related variables. IPT administration reduced 79% of the risk of TB incidence in PLHIV. Advanced research is required with prospective cohort designs with larger sample counts and multicenter, so this study can be generalized to the general population.

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