Factors That Reduce The Incidence of Lung Tuberculosis Other Than Isoniazid Preventive Therapy (IPT) in Latent Igra Positive HIV-TB Patients

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Abstract

Background. One crucial public health measure to stop persons living with HIV (PLWHA) from developing active TB is isoniazid preventative therapy (IPT). Only few hospitals in Indonesia continue to offer IPT.

Aim. The purpose of this study was to assess how IPT affected the incidence of TB in patients with latent HIV infection.

Method. This study uses a prospective cohort design and is quasi-experimental in design. Samples for the study were obtained by convenience sampling and the study was carried out in the inpatient and outpatient departments of UPIPI Dr. Soetomo Hospital. Latent IGRA positive HIV-TB patients who satisfied the inclusion requirements made up the samples.

Result. Of the 59 patients who finished the screening exam, 23 fulfilled the inclusion requirements for this study. Using the ELISPOT method, the IGRA T-SPOT.TB test yields 36 (64.29%) negative findings and 23 (35.18%) positive results. After six months of IPT

administration, analysis of the data revealed that the incidence of active pulmonary TB in latent HIV-TB patients was 0% in the IPT group and 0% in the non-IPT group. Antiretroviral medication used for more than four years and a CD4+ T lymphocyte count of more than 200 cells/μL were factors that contributed to the lack of pulmonary tuberculosis in both groups.
Conclusion. ARV used for more than four years and CD4+ lymphocyte count more than 200 cells/L contributing significantly in pulmonary tuberculosis incidence.
Keywords: HIV; IPT; latent TB; LTBI

Introduction

The World Health Organization (WHO) declared tuberculosis (TB) a global health emergency more than 15 years ago. Worldwide, 2 to 3 billion people have TB, an estimated 9 to 10 million people have TB, and 2 to 7 million TB patients die every year. Indonesia has the second highest TB burden after India. As can be seen, the number of people with TB or latent TB infection (LTBI) is very high [1]. HIV co-infection significantly increases the risk of TB. TB is the most common opportunistic infection and the leading cause of death in HIV/AIDS patients [2].

Isoniazid Preventive Therapy (IPT) is one of the important public health interventions by giving isoniazid (INH) to people with LTBI to prevent progression to active TB in PLWHA and has been recommended since 1998 by WHO [3]. Benefits of IPT given to HIV-Latent TB are to prevent progression to active TB, reduce the risk of TB by about 60-90%, provide a protective effect against TB for 3-5 years and has minimal side effects [2,4,5]. In Indonesia, based on the Minister of Health Regulation in 2014, in order to prevent the increasing prevalence of TB in PLWHA, all PLWHA who are after careful evaluation did not suffer from active TB and has a close contact with TB patients should be treated as LTBI with INH 300 mg/day for 6 months [6].

IPT implementation is very slow and delayed due to various obstacles including inadequate approach in excluding active TB and limited access to isoniazid (INH) due to the fear of drug resistance and some side effects such as hepatotoxic symptoms (nausea and vomiting), peripheral neuropathy, and skin rashes [4,6].

To date, IPT administration has not been performed simultaneously in different hospitals in Indonesia. In this study, the authors hope to provide insight into IPT as an active TB preventive treatment in HIV-infected patients to achieve the Millennium Development Goals (MDG) of reduce the incidence of tuberculosis in people infected with HIV.

Method

This research is a Quasi Experimental study with a prospective cohort design. The study was conducted in outpatient clinic and inpatient room UPIPI Dr. Soetomo Hospital in January-December 2018. The research sample was taken by convenience sampling. Samples were latent HIV-TB patients who met the inclusion criteria and willing to take part in the IPT program at Dr. Soetomo Hospital for 6 months. The inclusion criteria of this study were PLWHA on ARV therapy who were at least 21 years old, were not proven active TB based on TB screening: clinically negative, normal chest X-ray, negative GeneXpert sputum, diagnosed as latent TB with no active TB symptoms and had positive IGRA examination results, agreed to attend IPT activities and signed an informed consent. The exclusion criteria of this study were patients with extrapulmonary TB, abnormal liver function (SGOT and SGPT values >3 times the highest normal value), symptoms of peripheral neuropathy, and had an alcohol dependence. All study subjects were assessed for the IPT administration criteria, including HIV patients who did not have TB symptoms (cough, weight loss, night sweats), GeneXpert sputum examination, chest X-ray, SGOT/SGPT examination. If the clinical assessment, laboratory and chest X-ray of the subjects were not suspected for TB, IGRA examination would be conducted. If the IGRA result was positive, INH and vitamin B6 would be given, as well as routine laboratory tests of liver function (SGOT/SGPT) to patients for 6 months. Subjects would take INH drugs every month at UPIPI Outpatient Clinic Dr. Soetomo Hospital and would be asked whether they have clinical symptoms of TB, be done physical examination leading to suspicion of TB and side effects of INH. Subjects would be asked for clinical symptoms of TB, symptoms of IPT side effects and be examined for chest X-ray at the end of 6 months of IPT administration in the two groups, and the differences in the incidence of active pulmonary TB in the IPT and non IPT groups would be analyzed.

Subject characteristics data was analyzed between the IPT and non IPT groups using the Mann Whitney test and a significant value was obtained when $p<0.05$. Data on the incidence of active pulmonary TB in latent HIV-TB patients between the IPT and non-IPT groups for 6 months was analyzed descriptively. This study has received ethical approval from Dr. Ethics Hospital Dr. Soetomo Surabaya.

Result

From 59 HIV patients who had taken part within the IPT concealment test, 23 (35.18%) were inactive HIV-TB positive IGRA patients who met the consideration criteria and were willing to take an interest within the ponder by marking educated assent. A add up to of 23

individuals were randomly separated into two groups, 10 people within the IPT gather and 13 individuals within the non IPT group. One subject within the non IPT group was avoided since he may not be reached at the conclusion of the consider so he could not be assessed. The subjects of this consider were generally matured 31-40 years, male sex with hetero HIV chance factor, duration of enduring from HIV 0-5 years, duration of accepting ARV treatment 0-4 years, regimen of ARV Duviral-Neviral (60.0%) within the IPT group and FDC (69.23%) within the non IPT group, no smoking propensity and no history of TB contact, CD4+ T cell lymphocyte 500 cells/µL (50.0%) within the IPT gather. Subject characteristics can be seen in **Table I** below:

Table 1. Characteristics of research subjects

Characteristics	Group		P value
	IPT	Non-IPT	
Age (mean ± SD)	35.00±7.930	37.77±10.978	0.509
21 - 30 years	3 (30.0%)	5 (38.46%)	
31 - 40 years	4 (40.0%)	2 (15.38%)	
41 - 50 years	3(30.0%)	3 (23.08%)	
≥ 50 years	0 (0.0%)	3 (23.08%)	
Sex			
Male	6 (60.0%)	7(53.85%)	1.000
Female	4 (40.0%)	6 (46.15%)	
HIV risk factors			
Heterosexual	6(60.0%)	11(84.62%)	0.341
Homosexual	4(40.0%)	2(15.38%)	
Duration of suffering from HIV (mean ± SD)	4.835±3.573	4.365±3.188	0.067
0 - 5 years	8(80.0%)	11(84.62%)	
5.1 - 10 years	1(10.0%)		2(15.38%)
10.1 - 15 years	1(10.0%)	0(0.0%)	
Duration of ARV therapy (mean ± SD)	2.015 ± 2.493	2.316±2.510	0.082
0 – 4 years	5(50.0%)	11(84.62%)	
4.1 – 8 years	4(40.0%)	2(15.38%)	

Characteristics	Group		P value
	IPT	Non-IPT	
8.1 – 12 years	1(10.0%)	0(0.0%)	
ARV regimen			
AZT+3TC+NFP (Duviral-Neviral)	6(60.0%)	1(7.69%)	0.016
TDF+3TC+EFV (FDC)	4(40.0%	9(69.23%)	
3TC+TDF+ZDF	0(0.0%)	3(23.08%)	
Smoking			
Yes	3(30.0%)	5(38.46%)	1.000
No	7(70.0%)	8(61.54%)	
History of TB contact			
Yes	5(50.0%)	5(38.46%)	1.000
No	5(50.0%)	8(61.54%)	
CD4+ T Lymphocyte cell count (mean ± SD)	560.9±207.70	325.69±218.75	0.016
< 200 cells/µL	0(0.0%)	5(38.46%)	
200 – 349 cells/µL	1(10.0%)	2(15.38%)	
350 – 499 cells/µL	4(40.0%)	3(26.92%)	
> 500 cells/µL	5(50.0%)	3(26.92%)	

Characteristics of the think about subjects based on age, sex, HIV chance components, duration of suffering from HIV, duration of getting ARV treatment, smoking propensities, and history of TB contact within the IPT and non IPT groups appeared no significant differences between two bunches ($p>0.05$). Characteristics of think about subjects based on ARV sorts and CD4+ T lymphocyte cell check appeared significant differences between two groups ($p <0.05$).

Among the 22 subjects in the study, 10 in the IPT group and 12 in the non IPT group, the results showed no incidence of active pulmonary TB in either group after the 6-month assessment of IPT use, as shown in **Table 2** below :

Table 2. TB incidence in the ipt and non-ipt groups

Group	TB Incidence	
	Yes	No
IPT	0 (0.0%)	10(45.5%)
Non-IPT	0 (0.0%)	12(54.5%)
Total	0 (0.0%)	22(100.0%)

Based on the 2x2 table of 22 study subjects, 10 subjects in the IPT group and 12 subjects in the non-IPT group, the result of the analysis showed no difference in the incidence of active pulmonary TB in the two groups after evaluating for 6 months of IPT administration, as shown in **Table 3.** below:

Table 3. The incidence of TB

Group		TB Incidence	
		(+)	(-)
IPT	**(+)**	0	10
Non-IPT	**(-)**	0	12

Detection of latent TB in HIV patients showed 23 (35.18%) positive results and 36 (64.29%) negative results.The results of this study are consistent with the study by Sinaga et al. In Indonesia since 2017, which stated that from 88 latent HIV-TB patients, IGRA results were 26 (29.54%) positive and 62 (70.46%) negative [7]. It also similar with Elzi et al. 2011 study in Switzerland which found 25 (39%) positive IGRA results, 18 (28%) negatives and 21 (33%) indeterminate. Detection of latent TB in immunocompromised conditions was more difficult due to immune system destruction, so the IGRA sensitivity becomes low [8].

Discussion

HIV/AIDS is a disease that is still dominated by men, because sexual behavior such as clients of sex workers, the sexual relations between men and men and drug abuse (Drugs, Psychotropics and Additives). The results of this study are consistent with the data reported by the P2PL Directorate of the Ministry of Health of the Republic of Indonesia until December 2017 [9]. The age range of the most research subjects was during the productive age, which is

between 21-60 years. The HIV risk factors in this study were mostly heterosexual. In this study, all subjects were on antiretroviral (ARV) treatment. The maximum duration of antiretroviral therapy given was 0-4 years. This is consistent with the study of Bourgarit et al. A study conducted in France in 2015 showed that T-SPOT.TB was positive, TB was more common in patients who received ARV treatment for 1 to 6 years (76.0%) [10]. Most of the subjects had no smoking habit and no history of TB contact. The most used regimen of ARV was Duviral-Neviral (60.0%) in the IPT and FDC (69.23%) in the non IPT group. The CD4+ T cell lymphocyte count in the IPT non group was 500 cells/µL (50.0%). The results were in accordance with the study by Oni et al in 2010, which stated that the detection of IGRA on the high $CD4^+$ T lymphocyte cell count (> 200 cells/µL) was very good, so there were no false negative, borderline or indeterminate results.Although the sensitivity of T-SPOT.TB is not affected by the degree of immunodeficiency, positive T-SPOT.TB results tend to show a large number of spots with high numbers of CD4+ T lymphocytes [11].

In this study, the incidence of active pulmonary TB in latent HIV-TB patients 6 months after IPT administration was 0% in the IPT group and 0% in the non IPT group. The absence of pulmonary TB events in both groups is possibly because the incidence of latent HIV-TB that will reactivate to active TB is 5% -10% annually due to the weak cellular defense system of HIV patients [2,5]. The result of this study was in line with the research conducted in various countries, one of it is research at Wangaya Bali Hospital by Jarwa in 2017, which stated that the pulmonary TB incidence was 0 during 6 months of IPT administration [12]. The result of this study also supported by Hermans et al. research in 2016 which obtained tuberculosis incidence of 1.3 per 100 people per year during IPT administration and in the following year the incidence of TB was stable at 2.3 per 100 people per year [13].

A study conducted in Ethiopia in 2014 found zero incidence of active pulmonary tuberculosis, which is also consistent with the study conducted by Yirdaw et al, assessing the benefits of IPT and ARV on TB incidence. The TB incidence with the administration of IPT and ARV was 0.2 per 100 people per year, ARV only 0.32 per 100 people per year, while without ARV and without IPT 5.4 per 100 people per year. IPT administration for 6 months can prevent TB incidence up to 92%. The administration of IPT is effective in reducing the incidence of TB both if IPT is given alone, ARV is given alone or IPT is given together with ARV, tuberculosis incidence rate is 2.6 per 100 people per year [5].

Theoretically, administration of INH would sterilize latent microorganisms present in the body of Mtb-infected individuals, but the bacteriological incubation period may not fully correlate with the clinical incubation period. A more dynamic balance between the organism

and host immunity determines the progression of active disease. INH may play a role in altering this balance, which may help the host fight pathogens [14]. Research from various countries shows that the range of tuberculosis events after IPT overall administration is below 3 per 100 people years and in accordance with our study [5,12,13].

In this study, the absence of pulmonary TB event in the non IPT group is in accordance with the study by Sun et al in 2011 which showed that in latent HIV-TB patients diagnosed with IGRA T-SPOT.TB positive in ARV therapy and without IPT, the incidence of TB was only 0-1 of 64 people (0-1.5 per 100 per year). The incidence and total incidence of active TB in IGRA-positive HIV-infected patients ranges from 0 to 5 per 100 persons per year [15]. In line with studies in Brazil conducted by Golub et al in 2009, it is known that the incidence of TB in PLWHA after the administration of IPT and ARV was 0.8 per 100 people per year. This is lower than ARV only which was 1.9 per 100 people per year, reducing TB incidence by 92%, while TB incidence without ARV or without IPT showed a result of 4.1 per 100 per year [16].

In this study, the absence of TB events in both the IPT and non IPT groups is because both groups had received ARV therapy with good compliance and in a long period of time. Both groups received ARV therapy for a maximum range of 0-4 years. ARV therapy was given before and during IPT administration, which causes the body's immunity to increase. Several studies have argued that ARV therapy has a mechanism of action to prevent viral replication that gradually decreases the amount of virus in the blood, thereby increases the immune system in HIV sufferers by activating type 1 helper T cells, thus producing IFN cytokines ɣ. Furthermore, IFN ɣ together with IL-10 will induce NF-IL6 in macrophages that bind to the LTR of HIV, Suppressing HIV transcription in host cells and increasing the number of CD4+ T lymphocytes in HIV patients can prevent reactivation of latent to active tuberculosis [17].

In patients receiving ARV treatment for more than 6 months, the number of CD4+ T lymphocytes increases between 104 and 174 cells/μL during the first year after ARV treatment [16,18]. Early administration of ARV has proven to be clinically useful, beneficial for prevention, increase life expectancy and reduce HIV-related infections. Provision of ARV has become a WHO policy in TB prevention intervention that has been implemented on a large scale and is proven to reduce the incidence of TB in PLWHA by 80% [2,19]. This is also consistent with previous studies which showed a >90% reduction of TB incidence in the HIV patient population receiving ARV and IPT [20,21,22]. This is in accordance with our study where there was no active pulmonary TB incidence in the IPT and non IPT groups because they mostly have received ARV treatment in the range of 0-4 years,This increased the number of CD4+ T lymphocytes to more than 200 cells/μL. in both groups and reduce opportunistic infections,

one of which is the incidence of active pulmonary TB. After this research, we hope that the IPT program can be implemented in Dr. Soetomo Hospital Surabaya.

This study has the limitation that TST examination could not be done to support the diagnosis of latent TB together with the TSPOT.TB IGRA examination because PPD reagent was empty from the central distribution. Some investigations could not be done to help diagnose extra-pulmonary TB. The monitoring time to follow up the study subjects after IPT administration in the two groups was not long enough. The researchers only did the evaluation in 6 months during IPT administration because it was limited by time, energy and funds so that there were no active pulmonary TB events in the IPT and non-IPT groups.

Conclusion

ARV used for more than four years and CD4+ lymphocyte count more than 200 cells/L contributing significantly in pulmonary tuberculosis incidence.

References

1. Perhimpunan Dokter Paru Indonesia, “Pedoman tatalaksana infeksi TB laten Edisi 2016”, 2016, pp. 1-36.
2. C. Akolo, F. Bada, E. Okpokoro, O. Nwanne, S. Iziduh, E. Usoro, “Debunking the myths perpetuating low implementation of isoniazid preventive therapy amongst human immunodeficiency virus-infected persons”, *World J Virol*, 4(2), 2015, pp. 105-112.
3. WHO, “Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource- constrained settings”, Geneva: World Health Organization, 2015.
4. WHO, “Global tuberculosis program and UNAIDS: policy statement on preventive therapy against tuberculosis in people living with HIV”, Geneva: World Health Organization, 2012.
5. K. D. Yirdaw, D. Jerene, Z. Gashu, M. E. Edginton, A. M. V. Kumar, Y. Letamo, “Beneficial effect of isoniazid preventive therapy and antiretroviral therapy on the incisdence of tuberculosis in people living with HIV in Ethiopia”, *PlosOne*, 9(8), 2014, pp. 1-7.
6. Kesehatan Republik Indonesia, “Peraturan Kementerian Kesehatan Republik Indonesia No. 87 Tahun 2014 Tentang Pedoman Pengobatan Antiretroviral”, Jakarta: Kementerian Kesehatan Republik Indonesia, 2014.

7. F. Sinaga, Reviono, Harsini, "Validitas dan reliabilitas pemeriksaan TST dan T-SPOT.TB dalam mendeteksi infeksi TB laten pada penderita infeksi HIV", *FK UNS digital library*. 2017.
8. L. Elzi, I. Steffen, H. Furrer, J. Fehr, M. Cavassini, Hirschel, et al., "Improved sensitivity of an interferon-gamma release assay T-SPOT.TB in combination with tuberculin skin test for the diagnosis of latent tuberculosis in the presence of HIV co-Infection", *BMC infectious diseases*, 11(319), 2011, pp. 1-9.
9. Direktorat Jenderal Pengendalian Penyakit dan Penyehatan Lingkungan, "Laporan Situasi Perkembangan HIV-AIDS & PIMS di Indonesia Januari – Desember 2017", *Kementerian Kesehatan Republik Indonesia*, 2017.
10. A. Bourgarit, G. Baron, G. Breton, P. Tattevin, C. Katlama, C. Allavena, et al., "Latent Tuberculosis Infection Screening and 2-Year Outcome in Antiretroviral-Naive HIV-Infected Patients in a Low-Prevalence Country", AnnalsATS, 12(8), 2015, pp. 1138-1145.
11. T. Oni, J. Patel, H. P. Gideon, R. Seldon, K. Wood, Y. Hlombe, "Enhanced diagnosis of HIV-1-associated tuberculosis by relating T-SPOT.TB and CD4 counts", *Eur Respir J*, 36, 2010, pp. 594–600.
12. G. Jarwa, "Tidak ada kejadian tuberkulosis paru aktif selama 3 bulan pemantauan pasca pemberian pengobatan pencegahan isoniazid pada penderita HIV", *FK Udayana*, 2017.
13. S. M. Hermans, A. D. Grant, V. Chihota, J. J. Lewis, E. Vynnycky, G. J. Churchyard, "The timing of tuberculosis after isoniazid preventive therapy among gold miners in South Africa: a prospective cohort study", *BMC* Medicine, 14(45), 2016, 1-11.
14. R. Wood, L. G. Bekker, "Isoniazid preventive therapy for tuberculosis in South Africa: an assessment of the local evidence base", *S Afr Med J*, 104(3), 2014, pp. 174-177.
15. H. Y. Sun, P. R. Hsueh, W. C. Liu, Y. C. Su, S. Y. Chang, C. C. Hung, "Risk of active tuberculosis in HIV-infected patients in taiwan with free access to HIV care and a positive T-Spot.TB test", *Plos One*, 10(5), 2015, pp. 1-10.
16. J. E. Golub, P. Pronyk, L. Mohapi, N. Thsabangu, M. Moshabela, H. Struthers, "Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort", *AIDS*, 23(5), 2009, pp. 631-636.
17. W. M. El-Sadr, J. D. Lundgren, J. D. Neaton, F. Gordin, D. Abrams, R. C. Arduino, "CD41 count-guided interruption of antiretroviral treatment", *N Engl J Med*, 355, 2006, pp.2283–2296.

18. A. Mocroft, “Normalisation of CD4 counts in patients with HIV-1 infection and maximum virological suppression who are taking combination antiretroviral therapy: an observational cohort study”, *The Lancet* Journal, 370(9585), 2007, pp. 407-413.
19. WHO, “Guidelines on the management of latent tuberculosis infection”, Geneva: WHO, 2016.
20. World Health Organization, “WHO Three I’s Meeting: intensified case finding (ICF), isoniazid preventive therapy (IPT) and TB infection control (IC) for people living with HIV”, *Report of a Joint WHO HIV/AIDS and TB department meeting*, Geneva: World Health Organization, 2008.
21. A. Gupta, R. Wood, R. Kaplan, L. Bekker, S. Lawn, "Tuberculosis incidence rates during 8 years of follow up of an antiretroviral treatment cohort in south Africa: Comparison with rates in the community”, 2012, pp. 1-10.
22. J. L. Casado, S. Moreno, J. Fortun, A. Antela, C. Quereda, E. Navas, “Risk factor for development of tuberculosis after isoniazid hemoprophylaxis in Human Immunodeficiency Virus-Infected Patients”, *Clinical Infectious* Diseases, 344, 2002, pp. 386-389.