Effect of isoniazid preventive therapy on pulmonary tuberculosis activity in people living with HIV/AIDS at Wangaya hospital in Denpasar, Bali, Indonesia: A prospective cohort study

Ketut Suryana, Hamong Suharsono, Jarwa Antara, Ida Bagus Ngrah Rai

ABSTRACT

Background: Isoniazid Preventive Therapy (IPT) can reduce the Active Pulmonary Tuberculosis (APT) in People living with HIV/AIDS (PLWHA). IPT is recommended by the World Health Organization (WHO). It has not been implemented routinely in all countries.

Aim: To evaluate whether IPT in PLWHA reduces the APT at Wangaya Hospital, in Denpasar, Bali, Indonesia.

Methods: A prospective cohort study was conducted during October 2014 until November 2016. A total of 244 PLWHA were included in this study. The first group were 122 participants received antiretroviral therapy (ART) and IPT and 122 participants received only ART (second group). Cox regression analysis was employed to calculate effects in both groups and to identify predictor factors for active tuberculosis.

Keywords: Isoniazid, incidence, active TB, HIV/AIDS


INTRODUCTION

Isoniazid Preventive Therapy (IPT) is a public health interventions with isoniazid (chemoprophylaxis) for tuberculosis (TB) prevention in human immunodeficiency virus (HIV) infected individuals. Its reduces the Active Pulmonary Tuberculosis (APT), risk of first episode of TB occurring in individual exposed to infection, a recurrent episode of TB and with latent infection. IPT should be integrated with HIV treatment. The mortality rate was 89% reduction in Active Pulmonary Tuberculosis (APT) risk in South Africa. The recommendations for giving IPT to people living with HIV AIDS (PLWHA) were issued by International Union Against Tuberculosis and Lung Disease (IUATLD) and World Health Organization (WHO) in 1993, revised in 1998 and reinforced in 2004. Getahun et al in 2010 found no significant differences between the provision of 6 months and 36 months of IPT. The study objective was to evaluate the role of IPT for the reduction of APT in PLWHA.

MATERIAL AND METHODS

Study design and Participant

A prospective cohort study was conducted at Wangaya Hospital of Denpasar, Bali, Indonesia from October 2014 to November 2016. The total number of participants were 244, which divided into two groups; each group consisted of 122 participants. Consecutive sampling technique was followed. The participants who met the inclusion criteria were enrolled in the study until the required number of participants were met. The participants in this study were PLWHA who received ART and did not receive IPT who attended to Wangaya Hospital of Denpasar, Bali, Indonesia. The participants age ranges from 18 to 65 years with a study period from October 2014 to November 2016. Exclusion criteria included were participants with APT, liver disease, previous history with isoniazid hypersensitivity and severe alcohol dependence. Sample size is determined based on the sample formula for hypothesis testing different two independent proportions.

Correspondence to: Ketut Suryana; Department of Internal Medicine, Wangaya Hospital, Denpasar, Bali, Indonesia; ketutsuryana@gmail.com

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(two-sided test) with dichotomous independent variables and dichotomous dependent variables. The calculation using the estimated proportion of TB infection in the group without IPT (P2) by 40% and the estimated proportion of TB infection in the group with IPT (P1) of 20%. With α values = 5% and b values = 90%. The sample size is 109 samples with an estimated loss to follow up of 10%, the minimum sample was 120 samples for each group.

Variables and data sources
The main variables studied were non-APT. HIV diagnosis was based on national guidelines of clinical diagnosis and HIV therapy in Indonesia. The diagnosis of APT was based on symptoms and signs of TB which was performed every 28 days at the time of participants visit at the Merpati Clinic Wangaya Hospital. PLWHA who received ART were performed by TB screening. If there was a suspicion for TB (at least one of the positive symptom screening components), then a radiological and bacteriologic examination was done to identify the Acid Fast Bacilli (AFB). If confirmed, they were given Anti Tuberculosis drug (ATD) according to guideline. PLWHA who were not confirmed TB continued by clinical condition examination such as jaundice, nausea or vomiting, abdominal pain or hepatomegaly, isoniazid hypersensitivity and alcohol consumption. If there are any abnormality, samples were excluded. PLWHA who were not TB and without any clinical abnormality were divided into two groups as PLWHA who received ART, did not have APT and received IPT as a first group and PLWHA who received ART, did not have APT but refused IPT as a second group. First group received isoniazid 300 mg, 25 mg vitamin B6 and ART, while the second group received ART only. After a year post IPT administration, a TB screening was done for every participants. The study design is described in figure 1.

The monitoring was held every 28 days for 6 periods of administration and for 1 year after IPT administration. Each visit was held to identify adherence, as well as drug side effects including: nausea, vomiting, jaundice, dark colored urine, upper right abdominal pain, seizures, severe rashes, convulsions, psychosis and peripheral neuropathy. Important data were collected such as social demographic characteristics (age, sex and laboratory parameters). After a year of post IPT administration, TB screening was done for every participants. The study procedure was approved by The Institutional Review of Faculty of Medicine Udayana University, Sanglah Hospital of Denpasar, Bali, Indonesia with reference number 329/UN.14.2/Litbang/2016. Written informed consent was obtained from all the participants.

Statistical analysis
Descriptive test was performed to describe the participant characteristics. Kolmogorov-Smirnov test was used to test the data distribution. Variables with numerical or continuous scales and normally distributed are displayed in the form of mean and standard deviation. If the data is not normally distributed, it is displayed in median and range. For categorical scale variables the data is displayed in the form of relative frequency (number and percent), including in showing the incidence of APT in the study participants. Cox proportional hazard model was performed to determine the crude effect in both groups on the incidence of APT and adjusted Hazard Ratio (aHR) in both groups with age, sex and CD4 lymphocyte levels as the determinants variables. All data analysis was done using SPSS for Windows version 24.0 software.

Figure 1  Study design
**RESULTS**

A total of 244 participants / PLWHA (122 participants received ART and IPT 300 mg, 25 mg of vitamin B6 for 6 periods / 6 months). A total of 122 other participants only received ART. Both groups were followed for a year each, to confirm the occurrence of APT.

A total of 3 patients died during observation. A total of 5 patients from the IPT groups were lost to follow-up, in which 3 samples only reached the first month, 1 sample until the second month and 1 sample until the fourth month.

In this study both ART and Isoniazid were consumed according to the instructions of the researchers with very good levels of adherence. The demographic social characteristics are presented in Table 1. Majority of the participants were male for IPT and Non IPT group, with 55.7% and 56.6%, respectively.

Overall levels of CD4 lymphocyte participants in the groups were not normally distributed. Median CD4 lymphocyte levels was 182 cells/mL with a minimum of 1 cell/mL and a maximum of 1,177 cells/mL. In the IPT group the median CD4 lymphocyte was 296 cells/mL with a minimum of 12 cells/mL and a maximum of 1177 cells/mL, whereas in the non-IPT groups, a median was obtained: 64 cells/mL with a minimum of 1 cell/mL and a maximum of 550 cells/mL.

The incidence of APT during post-observation in both groups were 25 participants with an incidence rate of 6.83 per 100 person years. The number of incidence of TB in the IPT groups was 2 participants with an incidence rate of 1.09 per 100 person years and in the non-IPT groups as many as 23 participants with an incidence rate of 12.57 per 100 person years (Table 2).

PLWHA participants in this study who received ART only had a 10 times risk of tuberculosis compared with the groups receiving IPT, after adjustments for age, sex, and CD4 lymphocyte levels (aHR = 10.26; 95% CI: 2.15-48.99). In this study, gender, age and CD4 lymphocyte levels did not present as significant risk for the active pulmonary tuberculosis.

In this study the provision of IPT for 6 months gave a lower risk of APT compared to the group that did not get IPT, which had a higher risk of getting tuberculosis infection with an adjusted hazard ratio (aHR) of 10.26 (95% CI: 2.15-48.99) (Table 3).

**DISCUSSION**

Isonicotinic acid hydrazide (Iosinazid: INH) very specifically inhibits growth in some mycobacteria and is one of the most efficient antituberculous

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**Table 1** Demographic characteristic of study participants (N=244)

<table>
<thead>
<tr>
<th>Variables</th>
<th>IPT Group</th>
<th>Non IPT Group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Female</td>
<td>54 (44.3)</td>
<td>53 (43.4)</td>
<td>107 (43.9)</td>
</tr>
<tr>
<td>- Male</td>
<td>68 (55.7)</td>
<td>69 (56.6)</td>
<td>137 (56.1)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- No formal education</td>
<td>2 (1.6)</td>
<td>0 (0)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>- Elementary school</td>
<td>13 (10.7)</td>
<td>5 (4.1)</td>
<td>18 (7.4)</td>
</tr>
<tr>
<td>- Junior High School</td>
<td>22 (18.0)</td>
<td>34 (27.9)</td>
<td>56 (23.3)</td>
</tr>
<tr>
<td>- High School</td>
<td>69 (56.6)</td>
<td>73 (59.8)</td>
<td>142 (58.2)</td>
</tr>
<tr>
<td>- Academy</td>
<td>6 (4.9)</td>
<td>0 (0)</td>
<td>6 (2.5)</td>
</tr>
<tr>
<td>- University</td>
<td>10 (8.2)</td>
<td>10 (8.2)</td>
<td>20 (8.2)</td>
</tr>
<tr>
<td>Marital Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Marriage</td>
<td>102 (83.6)</td>
<td>95 (77.9)</td>
<td>197 (80.7)</td>
</tr>
<tr>
<td>- Single</td>
<td>16 (13.1)</td>
<td>20 (16.4)</td>
<td>36 (14.8)</td>
</tr>
<tr>
<td>- Widow/Widower</td>
<td>4 (3.3)</td>
<td>7 (5.7)</td>
<td>11 (4.5)</td>
</tr>
<tr>
<td>Age (year)</td>
<td>37 (23-64)</td>
<td>36 ±10</td>
<td>36.5 (20-64)</td>
</tr>
<tr>
<td>CD4 level (sel/mL)</td>
<td>296 (12-1177)</td>
<td>64 (1-550)</td>
<td>182 (1-1177)</td>
</tr>
<tr>
<td>APT in 1 year Post IPT</td>
<td>2 (1.6%)</td>
<td>23 (18.9%)</td>
<td>25 (10.2%)</td>
</tr>
</tbody>
</table>

CD4, cluster differentiation-4; APT: Active Pulmonary Tuberculosis; IPT, isoniazid preventive therapy.

**Table 2** Tuberculosis Incidence / 100 person years in participants (PLWHA) (n = 244)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Number of Active TB confirmed</th>
<th>Incidence of TB / 100 person Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPT</td>
<td>2</td>
<td>1.09</td>
</tr>
<tr>
<td>Non IPT</td>
<td>23</td>
<td>12.57</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>6.83</td>
</tr>
</tbody>
</table>

PLWHA, people living with HIV / AIDS; IPT, isoniazid preventive therapy; TB, tuberculosis

**Table 3** Multivariate Analysis of Cox proportional hazard model to Tuberculosis Incidence in participants / PLWHA (n = 244)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Category</th>
<th>Crude Hazard Ratio (95% CI)</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.60 (0.26-1.39)</td>
<td>1.82 (0.76-4.3)</td>
</tr>
<tr>
<td>Age (year)</td>
<td>≥ 36,5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&lt; 36,5</td>
<td>0.45 (0.19-1.05)</td>
<td>2.03 (0.86-4.77)</td>
</tr>
<tr>
<td>CD4 lymphocyte</td>
<td>≥ 182</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&lt; 182</td>
<td>0.24 (0.09-0.64)</td>
<td>1.26 (0.43-3.73)</td>
</tr>
<tr>
<td>IPT status</td>
<td>IPT</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Non - IPT</td>
<td>12.59 (2.70-53.43)*</td>
<td>10.26 (2.15-48.99)*</td>
</tr>
</tbody>
</table>

*p value < 0.05 was used as a significance limit, the precision value was determined with a 95% confidence interval value.

*significant (p< 0.05)
CD4, cluster differentiation-4; IPT, isoniazid preventive therapy
agents. INH inhibits a metabolism specific to mycobacteria (mycolic acid synthesis). These compounds are very long chain α-branched, b-hydroxy fatty acid characteristics of mycobacterial cell walls.\textsuperscript{1,4} The overall incidence of tuberculosis was 6.83 per 100 person years in 1 year. In the IPT groups the incidence of tuberculosis was 1.09 per 100 person years and in the non-IPT groups, the incidence of tuberculosis was 12.57 per 100 person years.

Study by Yirdaw et al., a retrospective cohort study in Ethiopia which published in 2014, with 5,407 participants, found that the incidence of TB in the IPT groups was 0.2 per 100 person years and the incidence of TB in the non IPT groups was 6.2 per 100 person years.\textsuperscript{15} Edessa et al (2014), a retrospective cohort study in Ethiopia with 185 participants, receiving ART and IPT, compared with 557 participants who only received antiretroviral drugs, found an overall incidence of tuberculosis of 6.37 per 100 person years. In the IPT groups of 1.80 per 100 person years while non IPT is 7.44 per 100 person years.\textsuperscript{16} Assebe et al (2015), a retrospective cohort study with 588 participants, the overall incidence of TB was 3.78 per 100 person years, in the group with IPT of 2.22 per 100 person years and in the non IPT groups of 5.06 per 100 person old.\textsuperscript{17} Quigley et al. (2001), a randomized controlled trial with 1053 participants found the overall incidence of tuberculosis was 3.6 per 100 person years.\textsuperscript{18} Hermans, et al (2016), a cluster-randomized study that included a community of mine workers with 18,520 participants found that the incidence of tuberculosis during the administration of IPT was 1.3 per 100 person years and after the IPT was 2.3 per 100 person years.\textsuperscript{19}

Several studies have shown no significant difference in the incidence of TB in the group who received IPT or who did not get IPT. Hawken et al. (1997) in a randomized controlled trial in Kenya found the incidence of TB in the IPT group was 4.29 per 100 person years and in the non-IPT group was 3.86 per 100 person years.\textsuperscript{20} Khawcharoenporn et al (2012) in a comparative prospective study in Thailand found the incidence of tuberculosis for 4 years was not significantly different between the IPT group and the non-IPT group (0.80 vs 1.76 per 100 person years).\textsuperscript{21}

In this study the high incidence of tuberculosis in the group non-IPT compared to the IPT groups showed an Isoniazid protective effect on tuberculosis. Participants of the non-IPT group were at higher risk for tuberculosis compared to the IPT groups. In the crude analysis, HR = 12.59 (95% CI: 2.70-53.43) was obtained and after adjustment, aHR in the non - IPT group was 10.26 (95% CI: 2.15-48.99). Besides the combination factors of ART and IPT that reduce the risk of tuberculosis infection, the role of adherence to ART and Isoniazid also plays an important role. Hawken, et al found that factors significantly associated with Isoniazid compliance include an explanation of Isoniazid from service providers (OR = 7.74; 95% CI: 3.144-19.058), feeling comfortable taking Isoniazid in front of people (OR = 5.981; 95% CI: 2.308-15.502) and those who come to the clinic regularly (OR = 4.0; 95% CI: 1.062-15.073).\textsuperscript{22}

Ayele et al, in a retrospective cohort study in Ethiopia, found that the combined effect of ART and IPT resulted in a 60% lower risk of tuberculosis or death compared to only those receiving only ART (HR = 0.40; 95% CI: 0.18- 0.87),\textsuperscript{19} Assebe et al, also found that the risk of developing tuberculosis was 2 times higher in the non – IPT groups compared to the IPT groups, aHR = 2.02 (95% CI: 1.04-3.92).\textsuperscript{1} Golub et al (2007) in a retrospective study in Brazil found a decreased risk of tuberculosis in participants receiving ART and IPT by 76% (aRH = 0.24; p <0.01).\textsuperscript{23} Likewise Jerene et al (2017) found that the use of IPT significantly reduced the incidence of TB (aHR = 0.06; 95% CI: 0.01-0.45).\textsuperscript{24}

In this study, we found sex, age and CD4 lymphocyte level are not associated with the increase of tuberculosis risk. Some studies reveal that risk factors or predictor factors that are significantly associated with tuberculosis include HIV infection (level of immunity: CD4 lymphocyte levels), INH, antiretroviral drugs, previous TB infection.\textsuperscript{25,26,27} Looking from the current study, there is a need for a large multicentric study to support the recommendation to the government that all of the health facilities could be implementation the IPT as a routine program.

CONCLUSION

In the non-IPT group the risk of APT incidence was higher than the IPT group. The treatment by ART plus IPT will reduced incidence APT significantly and also delayed HIV progression to AIDS than the ART only. Overall it means the implementation of IPT for PLWHA on ART as one of the strategies recommendation in TB preventive program is needed.

CONFLICT OF INTEREST STATEMENT

The authors declare that there was no conflict of interest in this research.
FUNDING

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AUTHOR CONTRIBUTION

Ketut Suryana are responsible in concepts and design, data acquisition, data analysis, manuscript preparation and editing. Hamong Suharsono, Jarwa Antara and Ida Bagus Rai are responsible in preparation, drafting, review, and approval of this manuscript.

REFERENCES


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